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COMPARISON OF WOUND HEALING IN VARIOUS NUTRITIONAL DEFICIENCY STATES

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THE INFLUENCE of various nutritional deficiencies on surgical risk has been under investigation in this laboratory for some time. Albino rats that have been acutely starved, chronically undernourished, and fed a pure carbohydrate (protein-free) diet have been subjected to various traumas, and mortality and longevity were observed. When a standardized surgical trauma was imposed upon such animals, at progressive decrements of body weight loss, no mortality appeared in the acutely starved and chronically undernourished animals and postoperative longevity was similar to that of the control animals.[4] Significant mortality (25.7 per cent) did ensue, however, in animals that were fed the protein-free diet for a long period of time.[5] It may be hypothesized that an increased deterioration of reparative processes in the animals fed the protein-free diet enhanced morbidity which, in turn, contributed to mortality. To test the hypothesis, wound tensile strengths were measured in the 3 nutritional deficiencies and the results compared.

METHODS

Male rats of the Holtzman Farms were used in all of the experiments. The animals weighed approximately 270 Gm. at the start of the studies. They were divided into experimental groups in random fashion, and the cages housing them were randomized throughout the laboratory. Ambient temperature during the experiments ranged between 70° and 78° F.

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The feeding and weighing methods have been previously described in detail.[4] Control animals were fed Purina Laboratory Chow and water ad libitum throughout the investigation. The animals maintained on a protein-free, pure carbohydrate diet were fed Domino Hostess Tablets* and water ad libitum. The animals lost weight steadily but slowly on this regime, reaching 55 per cent of their initial body weight in approximately 2 months. Acutely starved animals received water ad libitum. Food was removed from the animals' cages at 9:00 A.M. and the animals were weighed at noon of the day on which starvation was begun. This weight was taken as the initial body weight. The chronically underfed animals were fed Purina Laboratory Chow in decreasing daily amounts such that they would lose 45 per cent of initial body weight in 100 days. In this regime, the daily protein intake decreased from 2.8 to 1.4 Gm. Water was allowed ad libitum.

The chronically underfed and the sugar-fed animals were divided into sufficient groups so that wound tensile strength could be determined when average body weight of the groups had fallen to 70 to 75, 60 to 65, and 50 to 55 per cent of the initial body weight. At each weight level, rats on both types of diet had wounds made and their tensile strength tested 3 days later. These wounds were then resutured and tensile strength was determined again on the seventh day following creation of the original wound. Other animals of these dietary groups were wounded in the standard fashion and tensile strength was tested on the seventh day afterward, without intervening disruption of the wounds on the third day. These wounds are referred to as primary 7-day wounds. The acutely starved animals had standard wounds made on the day that starvation was begun, and their wound tensile strength was tested on the third day and again on the seventh day of starvation. Other groups of acutely starved rats had standard wounds tested only on the seventh day of starvation.

Wound tensile strength was determined by the method of Savlov and Dunphy.[7] Rats were anesthetized with ether and the abdomens were shaved. Septisol and merthiolate were used for skin preparation. Under sterile conditions, after the usual draping, midline laparotomy incisions 4 cm. in length were made. Lateral wire loops were then placed, having been previously threaded through intra-abdominal retaining tubes of polyethylene. The wounds were closed with 5 through-and-through sutures of No. 32 monofilament stainless steel wire. Prior to testing, these sutures were carefully removed. The tensile strength of the wounds is reported in the weight of water necessary to disrupt the wounds.

RESULTS

As each of the dietary insufficiencies imposed on the animals continued in time, considerable amounts of body weight were lost. The experiments were designed to test the tensile strength of standard wounds in each category of nutritional abnormality when animals reached 70 to 75, 60 to 65, and 50 to 55

*Domino Hostess Sugar Tablets supplied by the American Sugar Refinery Company.

per cent of their initial body weight with the exception of the acutely starved animals. The wounds in these animals were tested on the third and seventh days, and on the seventh day only following infliction of the standard wounds. This was the time interval used in the testing of all wounds. It will be noticed from Table I that in the groups maintained on abnormal diets there was a marked reduction in acquisition of tensile strength of the standard wounds as the animals lost weight. This progressive deficiency in wound tensile strength development as body weight is lost is most strikingly apparent in wounds tested on the seventh day.

TABLE I. TENSILE STRENGTHS OF PRIMARY 3-DAY, PRIMARY 7-DAY, AND RESUTURED 7-DAY WOUNDS AT INITIAL AND DECREASING PERCENTAGES OF INITIAL BODY WEIGHT IN ACUTELY STARVED, CHRONICALLY UNDERFED, AND SUGAR-FED RATS

INITIAL BODY WEIGHT (PER CENT)	DAY OF TESTING WOUNDS	SUGAR-FED		CHRONIC UNDERFED		ACUTELY STARVED	
		NUMBER OF ANIMALS	TENSILE STRENGTH (GM.)	NUMBER OF ANIMALS	TENSILE STRENGTH (GM.)	NUMBER OF ANIMALS	TENSILE STRENGTH (GM.)
100	3	12	150.6 ± 37.4	8	148.0 ± 49.2		
	(3)-7	12	909.0 ± 252.7	8	1019.0 ± 163.2		
	7	12	886.1 ± 192.5	7	761.0 ± 140.3		
82.9	3					10	153.0 ± 33.9
70-75	3	12	106.0 ± 67.0	7	79.0 ± 27.5		
	(3)-7	12	617.0 ± 207.7	8	520.0 ± 192.7		
	7	12	487.0 ± 209.4	7	543.4 ± 117.6		
60-65	3	12	79 ± 22.1	8	89 ± 54.6		
	(3)-7	10	422 ± 113.7	8	441 ± 74.2	10	662 ± 146
	7	12	441 ± 99.7	8	330 ± 76	10	535.5 ± 121.8
50-55	3	10	71.0 ± 24.4	8	72.4 ± 23.8		
	(3)-7	10	325.0 ± 90.0	5	192.0 ± 48.8		
	7	9	261.0 ± 63.6	5	227.0 ± 33.4		

Wounds tested on the third day, resutured, and tested again on the seventh day confirm the observations of Botsford,[1] and of Savlov and Dunphy,[6] who demonstrated that the resutured wound does not undergo a second lag period but continues to develop tensile strength as if it had not been disrupted. That this observation applied to wounds in animals which have sustained great losses in body weight secondary to the nutritional defects employed, as well as to wounds in normally fed animals, is also evident from Table I. While quantitative differences may be seen between certain of the experimental groups and between all experimental groups and the controls, qualitative trends remain the same throughout.

No statistically significant differences can be seen between wound tensile strength values of chronically undernourished and of sugar-fed animals (Table II). When the determinations in these 2 groups are compared with those in the acutely starved group, however, there is seen a statistical difference. The acutely starved animals exhibit greater tensile strength at the time of testing than do either of the other 2 groups. The probabilities of significance, using the Student "*t*" test for comparisons between groups, are shown in Table II.

TABLE II. COMPARISON OF WOUND TENSILE STRENGTH DIFFERENCES IN THE 3 TYPES OF NUTRITIONAL ABNORMALITY

COMPARISON BETWEEN:	INITIAL BODY WEIGHT (PER CENT)	TYPE OF WOUND	DAY OF TESTING	p
Chronic underfeeding and sugar-fed	100	Primary	3	$= 0.9$
	100	Resutured	7	$= 0.3$
	100	Primary	7	$0.1 < p < 0.2$
	70-75	Primary	3	$= 0.3$
	70-75	Resutured	7	$= 0.3$
	70-75	Primary	7	$= 0.7$
	60-65	Primary	3	$0.5 < p < 0.7$
	60-65	Resutured	7	$= 0.7$
	60-65	Primary	7	$= 0.02$
	50-55	Primary	3	$p > 0.9$
	50-55	Resutured	7	$0.02 < p < 0.05$
	50-55	Primary	7	$= 0.3$
Chronic underfeeding and acute starvation	70-75*	Primary	3	$p < 0.001$
	60-65	Resutured	7	$0.001 < p < 0.01$
	60-65	Primary	7	$0.05 < p < 0.1$
Sugar-fed and acute starvation	70-75*	Primary	3	$0.05 < p < 0.1$
	60-65	Resutured	7	$p < 0.001$
	60-65	Primary	7	$= 0.01$

*The acutely starved animals were at 82.9 per cent of their initial body weight on the third day of starvation and are, therefore, compared with animals at lower percentages of initial body weight. At 7 days, however, they are in the 60 to 65 per cent range of initial body weight as are the animals with whom they are compared.

TABLE III. WOUND TENSILE STRENGTHS IN THE 3 TYPES OF DIETARY ABNORMALITY

CONDITION	WOUND TENSILE STRENGTH AS PERCENTAGE OF INITIAL VALUE AT 60 TO 65 PER CENT OF INITIAL BODY WEIGHT	
	PRIMARY 7-DAY WOUND	RESUTURED 7-DAY WOUND
Acute starvation	65.0	68.7
Chronic underfeeding	40.1	45.7
Pure sugar feeding	53.5	43.8

TABLE IV. COMPARISON OF TENSILE STRENGTHS OF PRIMARY AND RESUTURED 7-DAY WOUNDS

INITIAL BODY WEIGHT (PER CENT)	CONDITION	TYPE OF WOUND	NUMBER OF ANIMALS	TENSILE STRENGTH (GM.)	SIGNIFICANCE
100	Control (sugar-fed)	7 day	12	886.1 ± 192.5	$p = 0.80$
		(3)-7 day	12	909.0 ± 252.7	
	Control (chronic underfeeding)	7 day	7	761.0 ± 140.3	$0.001 < p < 0.01$
		(3)-7 day	8	1019.0 ± 163.2	
75	Sugar-fed	7 day	12	487.0 ± 209.4	$0.1 < p < 0.2$
		(3)-7 day	12	617.0 ± 207.7	
	Chronically underfed	7 day	7	453.4 ± 117.6	$0.30 < p < 0.50$
		(3)-7 day	8	520.0 ± 192.7	
65	Sugar-fed	7 day	12	441.0 ± 99.7	$0.5 < p < 0.7$
		(3)-7 day	10	422.0 ± 113.7	
	Chronically underfed	7 day	8	330.0 ± 76.0	$p = 0.01$
		(3)-7 day	8	441.0 ± 74.2	
	Acutely starved	7 day	10	535.5 ± 121.8	$p = 0.05$
		(3)-7 day	10	662.0 ± 146.0	
55	Sugar fed	7 day	9	261.0 ± 63.6	$p = 0.1$
		(3)-7 day	10	325.0 ± 90.0	
	Chronically underfed	7 day	5	227.0 ± 33.4	$0.2 < p < 0.3$
		(3)-7 day	5	192.0 ± 48.8	

Wound tensile strengths as percentages of control (initial) tensile strengths in the 3 experimental situations, with members of the groups at 60 to 65 per cent of initial body weight, may be seen in Table III.

There is a suggestion that resutured wounds in animals at any level of body weight loss observed develop a slightly greater tensile strength on the seventh day than do wounds that are initially tested on the seventh day. Thus, there were 9 separate comparisons of tensile strengths in the various groups at the different levels of body weight loss. This represents the testing of wounds in 165 individual animals. Of the 9 comparisons all but two indicated that the measured tensile strength was greater in the resutured wound than in the primary wound. Three of the comparisons were statistically significant and 6 were not. These data are recapitulated in Table IV.

DISCUSSION

The observations reported are confirmatory of those of Botsford,[1] and of Savlov and Dunphy,[6] who demonstrated that the resutured wound does not undergo a lag period. The present observations, made in the presence of various nutritional deficiency states, indicate that the processes of wound healing, once initiated, continue even in the animals maintained on a protein-free diet. It is obvious that the amount of tensile strength that the wound develops in such animals by the seventh day is greatly depressed when compared to the control, but the process of wound healing seems to be a fundamental one and is set in motion even though the animals have no exogenous supply of protein and little remaining endogenous stores to utilize for major reparative functions.

It might be expected that animals having no protein in their diet would exhibit less efficient wound healing than those having suboptimal amounts of dietary protein. This view is especially appealing since it has been demonstrated that protein deficiency does interfere with normal wound healing,[2] and that sulfur-containing amino acids are important in healing processes.[3] It was, therefore, somewhat surprising to find that there was no difference in the tensile strength of 7-day wounds between chronically undernourished animals fed a balanced but calorically restricted diet and those fed a protein-free diet. A possible explanation of this observation may lie in the fact that the total serum protein levels in these 2 groups of animals are the same even though the serum protein concentrations are different between the groups. These observations are about to be published from this laboratory. The fact remains that the development of tensile strength is the same at the stated levels of body weight loss in either the chronically underfed rat or the sugar-fed rat.

That the acutely starved animals should be able to develop greater wound tensile strength at 7 days may be due to the fact that they probably can mobilize more precursor material for use by the healing site during the early period of healing, since they are not as debilitated during the first few days of starvation as are the chronically underfed and sugar-fed animals. Possibly also germane is the fact that acutely starved rats die with less loss of tissue substance than do the animals in the other 2 groups.[4, 5] Although this explanation is subject to some objective measurements, in its entirety it is speculative.

The data suggest that wounds tested on the third day and resutured and tested again on the seventh day may have greater strength than primary wounds tested on the seventh day. Specific experiments designed to test this implication should be conducted.

There is nothing in these observations to suggest that there is selectively enhanced morbidity due to impaired wound healing in rats on the protein-free diet inasmuch as the efficiency of their wound healing is in the same order of magnitude as that of the chronically undernourished animals. It is, therefore, unlikely that the increased mortality following surgical trauma previously observed in the sugar-fed rats,[5] is directly related to problems of wound healing or general tissue repair.

SUMMARY

The tensile strength of wounds of nutritionally deficient male albino rats was tested on the third day, and the wounds were resutured and retested on the seventh day following original wounding. The tensile strength of undisturbed 7-day wounds was also determined in similar animals. The nutritional deficiencies employed were acute starvation, chronic undernutrition, and maintenance on a protein-free (pure carbohydrate) diet. Wounds were tested in animals subject to these various deficiencies when they had deteriorated to 70 to 75, 60 to 65, and 50 to 55 per cent of their initial body weight, except in the acutely starved animals whose wounds were tested on the third and seventh days of starvation. The tensile strengths of all wounds declined steadily and significantly to low levels as body weight was progressively lost.

Wounds disrupted and resutured on the third day and tested on the seventh day healed without lag to the approximate tensile strengths of primary 7-day wounds. This phenomenon was present at all levels of the various nutritional deficiency states tested.

The wounds of the acutely starved animals developed greater tensile strength at 7 days than did those of the chronically underfed animals or those maintained on a protein-free diet.

The wounds of those rats fed the protein-free, pure sugar diet healed with as much tensile strength as did those of the rats fed the balanced but subcaloric diet.

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EFFECT OF TENSION ON HEALING OF APONEUROTIC WOUNDS

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INTRODUCTION

ALTHOUGH physical factors such as tension are known to affect the healing of wounds, there are few quantitative studies available on such influences. Surgeons generally have taught that the absence of tension during the early stages of wound healing is desirable. Borgstrom and Sandblom[1] found that skin wounds in rabbits healing under tension were significantly weaker at 5 days than control wounds without tension. Wounds of the entire abdominal wall in rats, on the other hand, healed with more tensile strength at 10 days, when the animals were exercised.[5] Mason and Allen[4] showed that when a healing tendon was immobilized throughout its healing period, it healed neatly, retaining its gliding function and having a minimum of reaction with surrounding tissues. However, such a tendon had less tensile strength than one in which motion was begun at 21 days, and the difference increased as healing continued. They stated that the tension had no effect during the exudative and fibroblastic phase but only during the maturation phase of the wound from 19 days on. Lounsbury[3] showed that tendons which healed with the tension of muscle tone, either from its own muscle or from another sutured to it, had more tensile strength than tendons of denervated muscles. This effect of tension was given histologic confirmation by Buck[2] who showed that the increased strength was accompanied by elongation and orientation of cells and fibrils in the direction of the tension.

In the present study the effect of tension applied at various times after suturing has been tested in fascial wounds in rabbits.

METHOD

Stock rabbits on standard diets were used. Under pentobarbital anesthesia, the lumbodorsal fasciae were exposed through a midline skin incision and a 10 cm. wound parallel to and 1.0 to 1.5 cm. from the spinous processes was made bilaterally through the aponeuroses down to the muscle (Fig. 1). Both wounds were sutured with 4-0 silk sutures placed 5 mm. apart and 5 mm. from the edge. A relaxing incision was made 2 cm. lateral to each primary wound, and one relaxing incision was sutured up in the same manner as the primary incision, either at the time of the first operation or at a later date. On the side

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where the relaxing incision was left unsutured, the fascia surrounding the wound was completely flaccid. On the other side tension was similar to that of normal fascia. This tension measured in 4 rabbits during anesthesia was 12 to 20 Gm. per centimeter. The lumbodorsal aponeurosis in the rabbit is fixed to the spinous processes of the vertebral column, so that tension from one side was not transmitted to the other.

To measure the tensile strength of the wound, the fascia was excised and the sutures were removed. The fascia was cut into 1 cm. strips perpendicular to the wound, discarding 0.5 cm. at each end and any portion of the wound obviously damaged in processing. This yielded five to nine 1 cm. strips. A small strip was saved for histologic study. Fig. 2 shows the excised fascia.

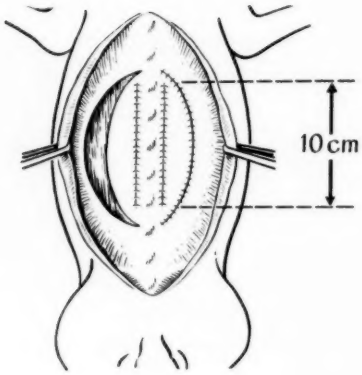

Fig. 1.

Fig. 2.

Fig. 1.—Diagram of operative procedure. Dorsal view of rabbit, with tension applied to wound on right side.

Fig. 2.—Excised fascia after 83 days. Tension was applied on the right side, which had nearly 3 times greater tensile strength (Table I) in spite of the appearance of disruption.

The tensiometer consisted of a balance mounted on a ring stand. One end of the fascia strip was attached to a clamp suspended from the center of one side of the balance and the other end to a clamp fixed to the ring stand directly below. On the opposite side of the balance, water was added at a rate of 17 to 20 Gm. per second, and the amount was recorded when the strip

broke. In all cases the strip broke at the wound quite suddenly. In each rabbit the difference in mean tensile strength of the two sides was analyzed for statistical significance.

A cross section of each wound was stained with hematoxylin and eosin, and with van Gieson stain. Pairs of wounds from each rabbit were compared for orientation of collagen fibers and fibroblasts and for blending of new fibrous tissue with the fascia.

RESULTS

There are two types of control wounds to compare with those under tension: wounds without tension, and those to which tension was applied at different intervals after wounding. In every case, comparison is made only between two wounds in the same rabbit. Wounds which healed under tension showed linear defects perpendicular to the wound, caused by tearing of the sutures and spread of the fascial edges; the intervening area was replaced by thin translucent tissue. The sutures lost their straight line relationship in the widely spread wounds and were scattered about in the regenerated area. The wounds healing without tension showed little change except for closure of the line of incision.

Group I. Tension on One Side and No Tension on the Other Throughout the Healing Period (Table I).—In the first 5 days there was essentially no difference in the tensile strength of the 2 wounds. In the next 2 weeks there was a rapid gain in tensile strength of the wound with tension, reaching a plateau at around 21 days with slower gain in strength thereafter up to 12 weeks. The wound without tension reached a plateau in 9 to 11 days and did not gain much more strength. From 3 weeks on, it maintained about 40 per cent of the strength of the wound healing with tension.

TABLE I. COMPARISON OF TENSILE STRENGTH OF WOUNDS HEALING WITH AND WITHOUT TENSION THROUGHOUT THE HEALING PERIOD

HEALING PERIOD (DAYS)	NUMBER OF RABBITS	MEAN TENSILE STRENGTH		PER CENT NO TENSION / TENSION	P*
		TENSION	NO TENSION		
5	3	104	95	92	0.60
8	3	465	309	67	0.05
10	5	1,007	682	68	<0.001
15	1	496	444	89	0.48
23	5	1,504	593	40	<0.001
43	2	751	362	47	<0.001
83	4	2,654	930	35	<0.001

*P—probability that the difference was due to chance. This was obtained by dividing the difference between means of observations at each time by the standard error of the difference.

Group II. No Tension on One Side Throughout the Healing Period, With No Tension on the Other Side for the First 7 Days.—After tension was applied, the wound gained rapidly in strength, becoming twice as strong as the wound without tension in 21 days (Table II).

Group III. Tension on One Side Throughout the Healing Period, With No Tension on the Other Side for the First 7, 14, or 21 Days of Healing.—When

tension was absent for the first week, the wounds did not significantly differ in strength (Table III). When tension was absent for 2 weeks, the wound was as strong at 3 weeks as the control with tension throughout, but at 6 weeks the control was stronger (Table IV). When tension was applied 3 weeks after wounding, the wound at 6 weeks was 75 per cent as strong as the control wound with tension throughout (Table V).

TABLE II. COMPARISON OF TENSILE STRENGTH OF WOUNDS HEALING WITHOUT TENSION THROUGHOUT HEALING PERIOD AND WOUNDS WITH TENSION APPLIED AFTER ONE WEEK

HEALING PERIOD (DAYS)	NUMBER OF RABBITS	MEAN TENSILE STRENGTH		PER CENT NO TENSION / LATE TENSION	P
		LATE TENSION	NO TENSION		
10	5	906	603	67	<0.001
21	6	1,087	601	55	<0.001
44	2	603	194	31	<0.001
62	1	933	361	39	<0.002
86	1	2,094	873	32	<0.001

TABLE III. COMPARISON OF TENSILE STRENGTH OF WOUNDS HEALING WITH TENSION THROUGHOUT AND WOUNDS HEALING WITH TENSION APPLIED AT ONE WEEK

HEALING PERIOD (DAYS)	NUMBER OF RABBITS	MEAN TENSILE STRENGTH		PER CENT LATE TENSION / FULL TENSION	P
		TENSION THROUGHOUT	TENSION AT 7 DAYS		
11	6	730	872	120	0.54
21	5	1,070	1,097	102	0.84
42	5	1,590	1,525	96	0.76

TABLE IV. COMPARISON OF TENSILE STRENGTH OF WOUNDS HEALING WITH TENSION THROUGHOUT AND WOUNDS HEALING WITH TENSION APPLIED AT TWO WEEKS

HEALING PERIOD (DAYS)	NUMBER OF RABBITS	MEAN TENSILE STRENGTH		PER CENT LATE TENSION / FULL TENSION	P
		TENSION THROUGHOUT	TENSION AT 14 DAYS		
21	5	929	855	93	0.72
45	6	2,119	1,492	70	<0.001

TABLE V. COMPARISON OF TENSILE STRENGTH OF WOUNDS HEALING WITH TENSION THROUGHOUT AND WOUNDS HEALING WITH TENSION APPLIED AT 3 WEEKS

HEALING PERIOD (DAYS)	NUMBER OF RABBITS	MEAN TENSILE STRENGTH		PER CENT LATE TENSION / FULL TENSION	P
		TENSION THROUGHOUT	TENSION AT 21 DAYS		
43	4	2,377	1,802	75	< 0.001

Histologic sections of wounds from Group II showed no consistent difference in the 2 sides. In Groups I and III, the wounds without tension showed sharp, often rolled fascial edges without blending with the new collagen fibers. The wounds with tension showed better orientation of the fibers and fibroblasts in the direction of tension (Figs. 3 and 4).

DISCUSSION

The data show conclusively that wounds which heal with tension are stronger than those that heal without it. This phenomenon is not altered by

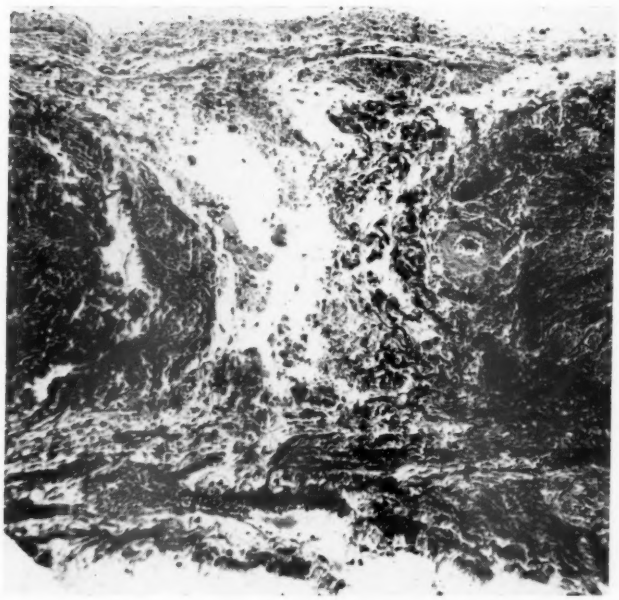

Fig. 3.—Wound 21 days old healing without tension. Note lack of orientation of collagen fibers between fascial edges (× 85).

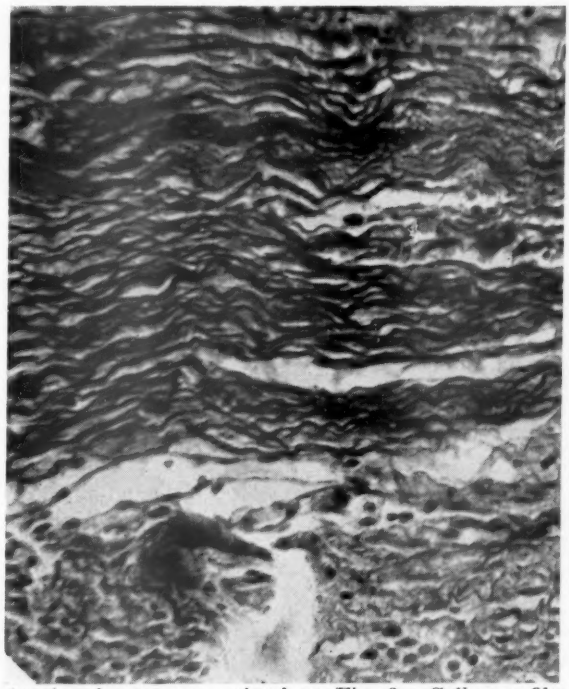

Fig. 4.—Wound with tension from same animal as Fig. 3. Collagen fibers are aligned across the wound (× 180).

delaying application of tension for 7 days. It is apparent that tension produces an orientation of collagen fibers in the direction of stress, but it is not readily determined how much of an increase in the total amount of collagen is present, because the original wound edges are separated irregularly. There was a wide range of tensile strength in wounds of similar age and tension state, as well as some difference in strips of the same wound. However, comparisons were made only between wounds in the same animal, so that nutritional and endocrine variations need not be considered.

CONCLUSIONS

1. Aponeurotic wounds which heal under tension have a greater tensile strength than wounds healing without tension in rabbits.

2. The effect of tension on tensile strength begins about the seventh day and reaches a plateau about the twenty-first day.

3. Application of tension to the healing wound after a period of up to 7 days has the same effect as if it were applied from the beginning.

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WOUND HEALING IN THE PARAPLEGIC PATIENT

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THOSE entrusted with the care of the paraplegic patient are regrettably familiar with the ease of decubitus development and the delay in healing in denervated areas of their patients. To the best of our knowledge controlled studies of healing in the paraplegic patient are not available in the literature. The fundamental question, is the problem in delayed healing due to general metabolic factors or does it represent a local phenomenon, begged for an answer. To seek the avenue of study we undertook to compare the rate of healing of skin defects in the normal and denervated areas of paraplegic patients. By choosing non-pressure areas, avoiding infection, and using the patient as his own control, many variable factors such as age, state of nutrition, anemia and so forth could be isolated from the experiment. The data of such a study should indicate the effect of denervation on healing.

The experimental method consisted of the sterile excision under 1 per cent procaine anesthesia of a circle of approximately 400 sq. mm. of full-thickness skin from the upper chest and the upper thigh. The operation was performed with a special tenplate with a razor-sharp edge specifically designed for this study. The wound was measured immediately after operation to allow for change in size consequent to elasticity. Measurements were then made again on the third day and weekly thereafter until final healing. The method used[1] could accurately measure wound areas of a few square millimeters.

Eleven male paraplegic patients with healing problems form the basis of this report. Table I lists the size of test wounds after operation, the days required for final healing, and the corrected days of healing calculated for a wound of exactly 400 sq. mm. This calculation neutralizes the difference in size of the original test wounds and thereby makes the data comparable.

The wide variation in healing rates within the control and denervated groups reflects differences consequent to age, state of nutrition, anemia, protein metabolism, and so forth and emphasizes the importance of using the patient as his own control. The significant data comparing corrected days of healing in the control and denervated areas are expressed as percentage difference plus or minus the control. Except for one patient that required 40 per cent more time to heal the denervated area, the remaining 10 patients show no significant difference in the rate of healing. This observation is at variance with the clinical impression

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TABLE I. COMPARISON OF HEALING RATES IN NONPRESSURE CONTROL AND DENERVATED AREAS

	DENERVATED AREA			CONTROL AREA			
PATIENT	SIZE OF WOUND (SQ. MM.)	DAYS OF HEALING	DAYS CORRECTED TO 400 SQ. MM.	SIZE OF WOUND (SQ. MM.)	DAYS OF HEALING	DAYS CORRECTED TO 400 SQ. MM.	PERCENTAGE + OR − CONTROL
DeB	375	59	63	358	66	68	−7%
FO	350	42	47	389	54	55	−14%
WI	381	49	50	394	44	44	−14%
EL	378	42	44	327	37	40	+10%
RI	440	31	28	581	37	20	+40%
KA	355	39	43	315	31	38	+13%
ST	359	35	39	364	35	38	+3%
WI	427	29	27	411	36	35	−20%
BU	364	42	46	398	47	47	−2%
RE	403	33	33	315	33	41	−19%
MO	369	52	56	343	50	57	−2%

held by physicians charged with the care of paraplegic patients. It is well known that paraplegic patients develop decubiti and that these ulcers heal slowly or fail to heal. How do we reconcile our data with these clinical facts? In the experiments reported, all in patients that had healing problems, we were careful to place our test wounds in nonpressure areas. This points to pressure trauma and ischemia unrelieved by pain warning as an important factor in the genesis and persistence of decubiti in the paraplegic patient.

SUMMARY AND CONCLUSION

In summary our data would indicate that the paraplegic patient can heal a wound in a denervated area as well as a similar wound in a control nondenervated area. The paraplegic patient cannot because of the lack of pain sensation protect himself against the destructive effects of local pressure ischemia. Denervation paraplegia is not a deterrent to healing but rather an invitation to ischemic pressure necrosis. The delay in healing observed in decubiti is not due to the failure to heal but rather to reinjury by painless pressure trauma.

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GRANULOMATOUS TUMORS AND NEOPLASMS OF THE COLON AND ANORECTAL ZONE IN VENEZUELA

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THE present study is based upon a review and analysis of 158,993 clinical histories of surgical patients admitted to the 5 most important public hospitals in Caracas during the 11-year period from 1946 through 1957. Upon these patients, 84,292 major operations were performed, and of this number only 188 had tumors of the colon and rectum (0.22 per cent). The rarity of these tumors in Venezuela is most remarkable and is still unexplained.

Of the 188 cases, 28 were inflammatory or granulomatous tumors of the colon, 30 were malignant neoplasms of the colon, and 130 were cancers of the anorectal zone—a proportion of 4 neoplasms of the rectum for each case of true cancer of the colon.

In Venezuela, with a population of 6 million, cancer occupies third place as a cause of death (8 per cent of the total number of deaths yearly). Whereas we have a proportion of cancer of other organs not unlike that prevailing in the United States, our percentage of cancer of the rectum and especially of the colon is extremely low. Women are affected more often than men in the proportion of 63 to 37 per cent. The average age of patients in our series was 43½ years.

According to Brill, 97 per cent of all tumors of the intestinal tract are malignant. This is not the case in Venezuela. Forty-eight per cent of tumors of the colon in our series were specific or nonspecific granulomata. In the presence of a tumor of the colon we never resort to radical surgery until we have established definitely the differential diagnosis between malignant lesions and granulomata by laboratory specific tests or biopsy.

The diagnosis in the 28 cases of inflammatory and granulomatous tumors in our series is shown in Table I.

TABLE I

DIAGNOSIS	NUMBER OF CASES
Nicolas-Favre's disease with invasion of the sigmoid and colon	12
Bilharziomas (bilharziasis)	11
Amebiomas	3
Nonspecific granulomata of cecum, colon and sigmoid	2

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The regions affected by these tumors are listed in Table II.

TABLE II

REGION	NO. OF CASES
Rectosigmoid	13
Sigmoid and descending colon	4
Descending colon	5
Splenic flexure	1
Transverse colon	2
Cecum and colon	2
Cecum	1

The granulomatous and inflammatory tumors in this country are almost always of parasitic origin, and they exhibit many of the characteristics of malignant tumors, inducing identical symptomatology and the same pathologic complications. They invade and infiltrate the neighboring tissues and organs, they cause stenosis and occlusions in the intestinal tract just as cancers do, and they may also kill the patient. Clinically, it is frequently impossible to differentiate between a granulomatous tumor and a cancer at the time of operation, and only an anatomicopathologic study can definitely decide the true nature of the tumor.

The symptomatology of tumors and pseudotumors of the colon depends upon their location. Those of the right half of the colon (right half of the transverse and ascending colon and cecum), due to the physiology and anatomy of the colic segment they occupy, are almost always characterized by diarrhea rarely alternating with occlusive episodes. Their effect upon the general health is marked, and on clinical exploration they are revealed as easily palpated voluminous tumors. Tumors of the left half of the colon (left half of the transverse and descending colon and sigmoid) are small tumors as a rule, difficult to palpate, and characterized clinically by occlusive episodes alternating sometimes with diarrhea.

Except Nicolas-Favre's disease, in which the tumor of the colon and sigmoid represents an extension of the lesions from the primary site, the rectum, the other inflammatory tumors, amebiomas, simple granulomas, and bilharziomas exhibit an evolution marked by 3 periods: (1) prodromic, with diarrhea accompanied by the symptoms induced by the etiologic agent (Bilharzia, amebae, and so forth); (2) a period in which a mass makes its appearance as well as the symptoms typical of its etiologic cause (at this stage, appropriate medical treatment may cause the tumor to regress and disappear); and (3) a period in which fibrosis replaces the inflammatory reaction in the affected tissues, and the pseudotumor becomes permanently established, does not regress, and induces the symptomatology characteristic of a true cancer.

The most important factor in arriving at a diagnosis of a granulomatous or inflammatory tumor is the presence of amebae or Bilharziae. A bilharzioma is caused by the reaction of the tissues surrounding the parasite itself or its ova. In the amebiomas, on the contrary, it is not the amebae directly that determine the tumor, but the ulcerations and traumatisms inflicted by the

amebae invading the intestinal mucosa with persistent and repeated attacks. Pathogenic bacteria come into play then, and a tumor develops as a consequence of inflammation and tissue reaction.

In the amebiomas operated upon by one of us (Pérez Carreño) we have never isolated the ameba from the tissues of the tumor, but the parasite was present at the time in the intestinal tract inducing frequent crises of diarrhea, and, in one case in which we had established an artificial anus, a violent attack of amebic dysentery developed and the amebae caused ulceration of the skin around the artificial anus. The diagnosis in cases of amebioma rests, therefore, on the concomitant presence of the clinical syndrome characteristic of amebic infection. There are no histopathologic lesions in the tumor itself typical of its amebic etiology.

Pseudotumors attack patients at an earlier age than do neoplasms of the large intestine. The general health of the patient is not so seriously impaired. Abdominal palpation is frequently painful. The x-rays usually fail to distinguish between malignant tumors and pseudotumors. A biopsy is the only test that will positively clinch the diagnosis.

Granulomatous and inflammatory tumors in an advanced stage require the same type of radical surgery that cancers do, but the prognosis is quite favorable and the final mortality rate does not exceed 10 per cent.

The usual localization of Nicolas-Favre's disease is the rectum and perirectum, but in the series of 55 cases operated upon at the Hospital Vargas in Caracas in the last 10 years, we found that in 12 (21.8 per cent) the disease had invaded the sigmoid, and in 6 of these 12 cases (50 per cent) the lesions had gone beyond the sigmoid infiltrating the descending colon in 3 cases and the transverse colon in 2. Furthermore, in 2 cases firm adhesions were found binding the rectosigmoid to loops of small intestine and the female pelvic organs. Of the 12 cases of Nicolas-Favre's disease attacking the large intestine, the poradenitis was associated with bilharziosis in one case and with intestinal tuberculosis in another.

The most frequent operations performed in our series of tumors of the colon were hemicolectomy with ileotransversostomy and cecostomy.

Only 2.5 per cent of malignant tumors are cancers of the anorectal zone in our hospitals. At the Oncologic Institute in Caracas, a hospital devoted exclusively to the treatment of tumors, 7,255 cases of tumor (benign and malignant) were operated upon in the last 10 years, and of this number 32 were cancers of the rectum (0.4 per cent, 11 men, and 21 women), but only 6 cases were cancer of the colon (0.08 per cent).

Anatomically, the rectum may be divided into 3 zones: (1) intraperitoneal or abdominal, (2) subperitoneal or pelvic, and (3) sphincteric or perineal.

In northern countries only 25 per cent of cancers of the rectum occur in the first 8 cm. of the rectum from the anal ring. In 75 per cent of the cases the tumors are supra-ampullar, affecting the high or intraperitoneal portion of the rectum. In our country the opposite occurs; the low localization (within the first 8 cm. of the rectum) was observed in 56 per cent of our series, and

only 44 per cent were in the high location. This difference in localization is important. Rectal cancers above the peritoneal reflection are propagated in an ascending direction, toward the sigmoid arterial arc and the angle of anastomosis between the last sigmoid and hemorrhoidal arteries, where it may remain stationary for a while; on the other hand, cancers of low localization invade early in ascending, descending, and lateral directions. These cancers are therefore more serious and the prognosis less favorable. Besides, cases of cancer of the supra-ampullar zone (high localization) lend themselves to sphincter-saving operations, which is not the case with cancers of the ampullar and anal zones.

An early diagnosis followed by an early radical operation are the important factors for the successful treatment of these cancers.

In our series of cases of cancer of the anorectal zone, the operative treatment employed is listed in Table III.

TABLE III

TREATMENT	PERCENTAGE OF PATIENTS
Abdominoperineal extirpation	61.6
Modified Kraske	7.5
Simple colostomy, ileostomy, in advanced cases	12.3
Inoperable cases	15.0

Most of the patients in our series belong to the humblest strata of society, and when they appeal for treatment at our charity hospitals they are usually admitted in very poor physical condition and so late that they generally have widely disseminated metastases.

The histopathologic diagnoses in our series of cancer of the anorectal zone are listed in Table IV.

TABLE IV

DIAGNOSIS	PERCENTAGE OF PATIENTS
Adenocarcinoma	66
Epithelioma spinocellularis	28
Solid carcinoma	1
Adenoacanthoma	1
Gelatinous carcinoma	3
Not specified	1

A high percentage of these cancers originate from benign adenomata. Polyposis and papillomata of the colon or rectum should be considered as precancerous lesions. It is also important to suspect cancer in long-standing cases of chronic ulcerative colitis.

The afore-mentioned precancerous lesions are very frequent in countries of the temperate zone but very rare in Venezuela. That may possibly explain, at least in part, the rarity of colon and rectal cancer in this country.

ACUTE SMALL BOWEL OBSTRUCTION WITH SIGMOID DIVERTICULITIS AND ITS MANAGEMENT

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ORDINARILY when one thinks of obstruction in connection with sigmoid diverticulitis one thinks of large bowel obstruction. Depending upon the underlying pathologic features of the situation, one may face a closed loop obstruction if the ileocecal valve is competent, or the small bowel may be involved in a retrograde fashion if the ileocecal valve is incompetent. The clinical and radiologic appearance of the disease will correspond to these findings. Clinically, the findings in closed loop large bowel obstruction are dilatation of the large bowel, constipation, no vomiting, and deep tympanitic percussion sounds, and occasionally one can outline the distended colon at the periphery of the abdomen. Radiographically, in closed loop large bowel obstruction the distention stops at the cecum, with maximum dilatation of the cecum and the ascending colon. When the ileocecal valve is incompetent the dilatation will extend to a verying degree into the small bowel. In these cases the clinical picture will show additional signs of small bowel obstruction, that is, vomiting and increased peristaltic sounds and rushes.

Occasionally, however, with sigmoid diverticultis one will find small bowel obstruction without evidence of the large bowel being obstructed. Usually adherence and kinking of the lower ileum to the sigmoid are the causative factors. The adherence may be caused by fibrinous exudate produced by the sigmoiditis. Perforation of the diverticulum may lead to abscess formation. In these cases the small bowel forming part of the abscess wall may become kinked. Obviously these complications will occur primarily in cases of acute diverticulitis or acute exacerbations of chronic recurrent diverticulitis. The clinical picture will be that of an acute intestinal obstruction on a mechanical basis, with the additional signs of acute sigmoid diverticulitis. These are pain in the left lower quadrant with or without rigidity, fever, elevated white blood cell count, vomiting, and abdominal distention with increased peristaltic sounds or rushes. The scout film of the abdomen will present distended small bowel loops, very frequently showing "stepladder" arrangement with very little or no gas in the large bowel.

It is interesting to note that this complication is rarely mentioned in the literature. Even less information is found on the management of this complication, which may create quite a difficult problem.[4] Littlefield[1] mentions that this

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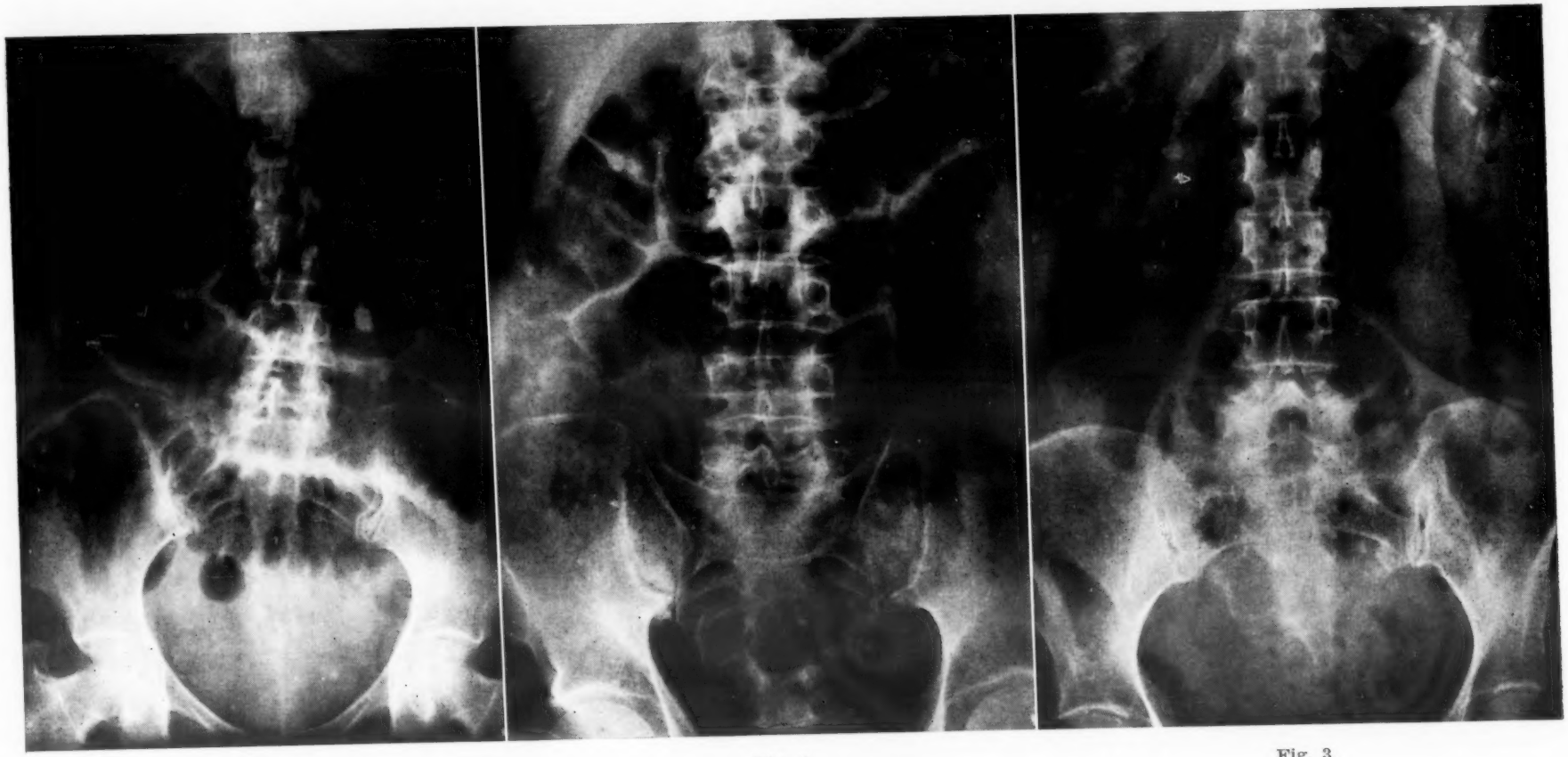

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1.—Mechanical obstruction of small bowel caused by perisigmoid abscess from perforated diverticulum.
Fig. 2.—Perisigmoid abscess from perforated diverticulum causing mechanical small bowel obstruction.
Fig. 3.—Obstructed small bowel caused by fibrinous peridiverticulitis of sigmoid.

complication is an indication for emergency surgical intervention. Morton,[3] reviewing 111 cases of diverticulitis, found 3 cases with small bowel obstruction. Mayo and Blunt,[2] reviewing 202 cases of diverticulitis with complications, do not mention this complication at all. A review of publications on diverticulitis in the *American Journal of Roentgenology and Radiology* between 1948 and 1956 failed to disclose any material dealing with this specific complication.

A review of 112 cases of diverticulitis treated at the Rochester General Hospital revealed 4 such cases. Three of these cases form the basis of this publication.

CASE REPORTS

CASE 1.—H. R. (No. 022463), a 63-year-old woman, had repeated attacks of diverticulitis treated conservatively since 1952. She was admitted July 29, 1957, with the history of nausea, vomiting, and low abdominal pain associated with a temperature of 100 to 101° F. On admission her temperature was 102.8° F. The abdomen was distended with local and rebound tenderness over the left lower quadrant. The bowel sounds were hyperperistaltic. A radiograph of the abdomen revealed small bowel obstruction of the mechanical type (Fig. 1). Parenteral antibiotics and parenteral fluid therapy were started. Intestinal decompression with a Cantor tube was not successful and surgery was performed on Aug. 2, 1957. Through a left McBurney incision a perisigmoid abscess was evacuated and drained. The adhesions between the ileum and the sigmoid were carefully freed and a transverse colostomy was done. The recovery was uneventful except for mild myocardial failure which responded to the usual treatment. She was readmitted to the hospital on Jan. 20, 1958. The diverticultis-containing segment of the sigmoid was resected. The colostomy was closed on Feb. 4, 1958, and she was discharged from the hospital on Feb. 13, 1958.

CASE 2.—R. G. B. (No. C71297), a 65-year-old male was admitted for crampy abdominal pain of 5 days' duration. He had no previous history of gastrointestinal symptoms. On admission his abdomen was distended with increased peristalsis but no rigidity. The left lower quadrant was tender with rebound tenderness. His temperature was 100° F. and the white blood cell count was 9,100. The flat plate of the abdomen showed distended small bowel loops with beginning "stepladder" pattern (Fig. 2). Conservative management was started with intestinal intubation and suction, and parenteral antibiotics and intravenous fluid therapy were given. Two days later he developed severe abdominal pain with marked tenderness, rigidity, and questionable mass in the lower quadrant. It was felt that he developed an abscess from a ruptured diverticulum. Surgery was performed on Aug. 26, 1957. Through a left McBurney incision a perisigmoid abscess was drained, the kinked adherent small bowel was freed carefully, and a transverse colostomy was done. Recovery was uneventful and he was discharged on the twelfth postoperative day. He was readmitted on Oct. 29, 1957. The sigmoid segment with diverticulitis was resected. At this time also a small abscess was found between the sigmoid colon and the urinary bladder. One week later the colostomy was closed and the patient was dismissed from the hospital on Nov. 15, 1957.

Both of these cases demonstrate the management of small bowel obstruction with abscess formation. First, a conservative trial with antibiotics and intestinal decompression was instituted. Since these were unsuccessful, the direct approach of the problem with draining the abscess, freeing the small bowel, and performing a complementary transverse colostomy was chosen. There was enough fibrin around the area of perforation to cause adherence of the drain to the area of perforation, which prevented leakage into the peritoneal cavity.

CASE 3.—M. M. (No. 8946), a 79-year-old woman, was admitted to the hospital on Feb. 16, 1957, with crampy abdominal pain of 48 hours' duration accompanied by nausea and vomiting. In the past she had had several episodes of pain in the left lower abdominal quadrant. On admission her abdomen was found to be distended mostly in the left lower quadrant where a soft tissue mass which felt like small bowel matted together was palpable. The bowel sounds were increased. The white blood cell count was 12,000. Her temperature was 101° F. A flat plate of the abdomen showed a distended loop of ileum (Fig. 3). A barium enema showed diverticulitis of the sigmoid colon. The obstruction subsided with antibiotics and conservative management. She was discharged from the hospital on Feb. 27, 1957.

This case was treated conservatively with only antibiotics and restoration of fluids and electrolytes. Complete resolution of obstruction resulted.

DISCUSSION

The prerequisite of proper handling of this complex situation is its prompt recognition. The management of this condition may be an extremely difficult one, primarily because it is a complication of an acute phase of diverticulitis. Obviously transverse colostomy alone will not be the answer to this problem. Diverticulitis is the primary cause for the obstruction, but it is the small bowel that is obstructed, and the problem is to relieve the small bowel obstruction and also to handle the diverticulitis. The relief of the small bowel obstruction can be accomplished in several different ways depending upon the underlying pathology. In general, one should always start out with conservative measures: antibiotic therapy, intestinal decompression, and restoration of fluid and electrolyte balance. If the obstruction was primarily caused by mild fibrinous perisigmoiditis, the intestine will free itself in the majority of the cases with intestinal intubation and decompression. After decompression the re-established peristalsis may be strong enough to rid itself of the adhesions. Occasionally when there is very little fibrin present often causing only incomplete obstruction of the small bowel. This may release itself without intubation. In such cases, antibiotics and observation may be all that is necessary. These cases will present themselves clinically with signs and symptoms of complete or incomplete small bowel obstruction and mild signs of diverticulitis. There will be some pain in the left lower quadrant with some tenderness, slight fever, not much rigidity, and no palpable firm masses. The white blood cell count may be moderately increased or may be completely normal since most of the people affected with this disease belong to the older age group. If the decompression was successful and the sigmoiditis subsides, one can proceed at a later date with a one-stage resection of the affected area of the sigmoid. Operation will be indicated if decompression is not accomplished within 48 hours or the obstruction recurs after temporary decompression. The fibrinous adhesions attaching the kinked loop to the sigmoid are carefully separated. In case the diverticulitis is not severe and the proximal and distal colon segments next to the diseased segment show no signs of inflammation, primary resection can be done. If the inflammation is quite extensive with much edema of the neighboring colon segments, transverse colostomy is preferable, with resection of the diseased sigmoid performed at a later date. Abscess formation will result in marked

pain and rigidity in the left lower quadrant with high fever and a palpable firm mass in the sigmoid area. The management of these cases is difficult and requires the most judgment. Closely watching the patient, one can try intestinal decompression again if the situation permits it. Operation will be mandatory if the patient's condition deteriorates or the decompression proves unsuccessful within 48 hours. Here again transverse colostomy alone will not be the answer. One will have to tackle the local situation as well. Adequate parenteral broad-spectrum antibiotic therapy should be started with intravenous fluids and electolytes. If there is no subsidence of the symptoms and abscess formation is obvious, the abscess cavity is emptied through a left McBurney incision. After completely emptying the abscess cavity, its wall can be exposed and the kinked small bowel loop visualized without difficulty. Then after the pus is adequately removed with suction from the cavity, the kinked small intestinal loop can be freed up from the usually loose fibrinous adhesions without much difficulty. The area of perforation is usually well sealed off by the time of surgery, and the seal will not be disturbed if the bowel is separated with great care. In all instances a drain should be inserted and this in itself will seal off any perforation that may be present. Most of the perforations that are present in cases of localized abscess formations are quite small and well surrounded with fibrin that seals the perforation rapidly. Diverting transverse colostomy is then performed. Intestinal suction is continued with the antibiotics and intravenous fluid therapy. The obstruction usually resolves itself rapidly. At a later date sigmoid resection can be done and the colostomy can be closed.

SUMMARY

The pathologic, clinical, and radiologic picture of acute small bowel obstruction with diverticulitis was presented. One hundred and twelve cases of diverticulitis were reviewed and 4 cases of small bowel obstruction with sigmoid diverticulitis were found. The different causes of small bowel obstruction were discussed and the treatment based upon these causes was given.

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DUODENAL OBSTRUCTION APPEARING AFTER PALLIATIVE BILIARY DIVERSION FOR PANCREATIC CARCINOMA

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TOTAL duodenal obstruction, at an interval following palliative cholecystojejunostomy for inoperable pancreatic carcinoma, was recently encountered in 2 patients admitted to this institution. Palliative gastrojejunostomy was done in each case. Because inoperable pancreatic carcinoma that obstructs the biliary tract is not infrequently encountered, and since it is usually dealt with by cholecystoanastomosis alone, this experience prompted a review of the palliative biliary diversions done at this institution during the previous 10 years.

Thirty-four patients with inoperable primary pancreatic carcinoma were admitted between January, 1947, and July, 1957. Twenty-eight of these patients underwent laparotomy, whereas definitive diagnosis was made in 6 patients at autopsy (Table I). Of the 28 patients subjected to laparotomy, 8 showed no evidence of biliary or gastrointestinal obstruction and, consequently, no palliative procedures were employed. Two patients presented with duodenal obstruction only and were palliated by gastrojejunostomy. Eighteen patients presented biliary obstruction only, showing no evidence at laparotomy of duodenal obstruction, and palliative biliary diversion was effected in all. Six of these 18 patients developed duodenal obstruction subsequent to the biliary diversion. Palliative gastrojejunostomy in 5 of these patients was followed by complete relief of their presenting signs and symptoms.

TABLE I. 34 CONSECUTIVE CASES OF INOPERABLE PANCREATIC CARCINOMA

1. Diagnosis by autopsy	6
2. Diagnosis by laparotomy and biopsy	28
A. No biliary or duodenal obstruction	8
B. Duodenal obstruction only	2
C. Biliary obstruction only	18
Died without duodenal obstruction	12
Died with duodenal obstruction	1
Palliative gastrojejunostomy prior to death for duodenal obstruction	5

CASE REPORTS

CASE 1 (No. 483468).—A 39-year-old man was admitted on June 23, 1948, with a one-week history of postprandial cramping, epigastric pain, nausea, and vomiting of bile-stained, recently ingested food. Six weeks prior to admission the patient underwent surgery elsewhere for obstructive jaundice. At that time there was noted obstruction of the common

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bile duct by a mass within the head of the pancreas. Histologic examination of an excised regional lymph node showed metastatic adenocarcinoma. A palliative cholecystoduodenostomy was carried out, following which the jaundice subsided and the patient remained symptomatically well until the onset of the present symptoms. Examination at the time of the present admission revealed dehydration and questionable icterus of the sclerae. The abdomen was distended and tympanitic in the epigastrium and left upper quadrant. There was a well-healed upper abdominal operative incision. The icterus index was 18. The vomitus contained recently ingested food which was strongly bile stained. Gastric aspirations were carried out twice daily with persistent gastric residuals in the range of 1,800 to 3,500 c.c. Exploratory laparotomy was performed on June 28 under continuous spinal anesthesia. Posterior gastrojejunostomy, liver biopsy, and biopsy of a large mass occupying the head of the pancreas, 5 by 5 by 8 cm., were carried out. Histologic examination of the pancreatic mass revealed it to be adenocarcinoma. The postoperative course was benign and the patient was discharged on Aug. 2, 1948, able to eat a general diet with minimal discomfort.

CASE 2 (No. 481408).—A 37-year-old woman was admitted on Jan. 31, 1952, with a 2-week history of progressive, painless jaundice during which time she noted that her urine became dark and her stools almost colorless. Physical examination revealed moderately severe icterus but was otherwise not remarkable. Icterus index was 125; alkaline phosphatase, 12.4 Bodansky units; cephalin-cholesterol flocculation 3+; and there was 2+ bile in the urine. The stools were not acholic. After a short period of medical observation, during which the above findings did not change, surgical consultation was sought and exploration advised. At exploratory laparotomy a mass within the pancreatic head was found to be obstructing the common bile duct. The duodenum was opened to ensure that this was not carcinoma of the ampulla of Vater, the mass was biopsied, and a tube cholecystostomy was carried out. The histologic diagnosis was carcinoma of the pancreas. The patient did well for several weeks and the cholecystostomy tube was then removed. Subsequently a remittent fever appeared and icterus recurred. Exploratory laparotomy was again performed on April 28, 1952, at which time a lesser omental abscess was drained and a cholecystojejunostomy was carried out. The postoperative course was benign and the patient was discharged improved on May 16, 1952.

The patient was symptomatically well until January, 1954, when she was admitted with a 3-week history of postprandial nausea, vomiting of recently ingested food, and a recent weight loss of 12 pounds. Physical examination and laboratory findings were not remarkable. Gastrointestinal radiography revealed a postbulbar narrowing of the duodenum and a markedly distended duodenal bulb. Exploratory laparotomy revealed a marked compression of the second duodenum by a large mass arising in the head of the pancreas and multiple, contiguous lymph-node metastases. Posterior gastrojejunostomy with biopsy of several regional lymph nodes was carried out. The lymph nodes showed metastatic disease on histologic examination. The postoperative course was benign and the patient was discharged improved on Feb. 7, 1954, able to eat a general diet without discomfort.

CASE 3 (No. 545791).—A 40-year-old man was admitted on Oct. 12, 1954, with a 20-day history of progressive, painless jaundice, dark urine, and acholic stools. Physical examination revealed intense icterus, hepatomegaly, and a firm globular mass inferior to the liver edge consistent with a palpable gall bladder. Laboratory findings were consistent with the existence of extrahepatic biliary obstruction. Stools were negative for occult blood. At exploratory laparotomy a 6 cm. diameter, stony hard mass was found within the head of the pancreas which was obstructing the common bile duct. Many enlarged, hard, periaortic nodes were palpable. Palliative cholecystojejunostomy was performed and the patient was discharged with diminishing jaundice on Oct. 31, 1954. He did well until January, 1955, when he was readmitted with a 3-week history of nausea and vomiting of recently ingested food and fluid. Gastrointestinal radiography revealed complete obstruction of the second portion

of the duodenum. At laparotomy the neoplasm was found to have produced marked periduodenal involvement. Palliative gastrojejunostomy was performed. The postoperative course was benign and the patient was discharged on Feb. 2, 1955, able to eat a general diet without difficulty.

CASE 4 (No. 492247).—A 53-year-old man was admitted on May 6, 1954, with a 2-week history of upper abdominal pain, progressive jaundice, and weight loss. The urine had become dark and the stools acholic. Physical examination revealed only intense icterus and the laboratory findings were consistent with the existence of extrahepatic biliary obstruction. At exploratory laparotomy the pancreas was found to be diffusely enlarged and hard, and the common bile duct was dilated. A gross diagnosis of pancreatic carcinoma was made and choledochoduodenostomy was done. Except for persistent back pain the patient did well until October, 1954, when he developed epigastric pain, nausea, and occasional vomiting. He was readmitted and investigation revealed a duodenal ulcer with 50 per cent retention of the barium meal at 4 hours. The patient was treated conservatively and he improved. On Jan. 12, 1955, he was again readmitted because of vomiting of recently ingested food during the previous 2 weeks. Large 4-hour postprandial residuals were found on gastric aspirations. Exploratory laparotomy revealed considerable extension of the mass in the pancreas, with constriction of first duodenum. A palliative gastrojejunostomy was performed. The postoperative course was benign and the patient was discharged on Jan. 27, 1955, able to eat a general diet.

CASE 5 (No. 528165).—A 69-year-old man was admitted on Oct. 10, 1952, with a 5-week history of severe cutaneous pruritus and progressive, painless jaundice of 3 weeks' duration. The urine had become dark and the stools acholic during this time. Physical examination revealed intense icterus, hepatomegaly, and an enlarged, palpable gall bladder. Laboratory findings were consistent with the existence of extrahepatic biliary obstruction. Exploratory laparotomy on October 14 revealed obstruction of the common bile duct by a firm, irregular mass occupying the head and a portion of the body of the pancreas. The mass was biopsied and palliative cholecystojejunostomy was performed. Histologic examination revealed adenocarcinoma of the pancreas. The postoperative course was benign, the jaundice subsided rapidly, and the patient was discharged on Oct. 29, 1952. The patient regained his usual weight and was symptomatically well until January, 1954, when he was readmitted with a 3-week history of upper abdominal cramping pain, nausea, vomiting, and a weight loss of 20 pounds. Gastric aspirations revealed a 4-hour postprandial gastric residual. Upper gastrointestinal roentgenography showed marked annular constriction of the second duodenum with virtually complete obstruction of gastric outflow. Exploratory laparotomy revealed obstruction of the second duodenum by an extensive mass arising within the head of the pancreas. Palliative gastrojejunostomy was performed. The postoperative course was benign and the patient was discharged on Feb. 10, 1954, able to eat a soft diet without difficulty.

DISCUSSION

The not uncommon incidence of carcinoma of the pancreas,[2] the infrequency with which resection of this lesion is feasible, and the high incidence of involvement of the pancreatic head[3] consort to make consideration of palliative biliary diversion a fairly common surgical problem. Since patients with this disease who present biliary obstruction usually do so before they are terminal,[1] palliative surgery is usually employed.

The experience reported here is not sufficiently large to significantly establish the incidence of duodenal obstruction appearing between palliative biliary diversion and death in carcinoma of the pancreas. The experience is such, however, to indicate that this occurrence is surely more than a rarity. No consideration

of this problem was found in the literature. Maingot[4] indicates that he adds gastrojejunostomy to biliary diversion when he encounters constriction of the duodenum by the lesion. Cattell[1] mentions the addition of gastrojejunostomy to biliary diversion only when biliary obstruction and duodenal obstruction are coexistent.

It is to be noted that the patients reported here showed no evidence of duodenal obstruction at the time of their biliary diversion, were not terminal at the time of onset of duodenal obstruction, and were relieved of their presenting signs and symptoms by palliative gastrojejunostomy.

The average life span of patients found to have inoperable carcinoma of the pancreas is 9 months.[1] In spite of this brief life expectancy, if a palliative procedure has been undertaken for biliary obstruction, there seems to be no rationale for withholding a further palliative procedure should duodenal obstruction intervene before the terminal phase. Considered in light of the experience reported here, this suggests the routine addition of gastrojejunostomy to palliative biliary diversion when exploratory laparotomy reveals biliary obstruction by pancreatic carcinoma.

SUMMARY

1. Of 18 consecutive palliative biliary diversion operations for inoperable carcinoma of the pancreas, 5 patients subsequently required palliative gastrojejunostomy for duodenal obstruction which appeared prior to the terminal phase of the disease.

2. Consideration is raised of the routine addition of gastrojejunostomy to palliative biliary diversion for inoperable pancreatic carcinoma that obstructs the extrahepatic ductal system.

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REFLUX PRESSURE STUDIES ON THE ILEOCECAL VALVE OF DOGS AND HUMANS

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THE anatomy and physiology of the ileocecal valve have been studied extensively. It has been shown by Henricksen and Ivy[3] and Buirge,[1] as well as others, that the ability of the ileocecal valve to prevent reflux from the cecum to the ileum is based upon two factors: first, the anatomical structure of the valve produces a mechanical block to reflux, and, second, there is a physiologic sphincter located within the cecal portion of the terminal ileum. Buirge had the unique opportunity of studying an exteriorized ileocecal valve and found that it was a physiologic sphincter which responded to various stimuli.[1] The same author has reported that 46 per cent of a series of 500 human ileocecal valves examined at autopsy had a significant anatomic variation with the implication that a good percentage of these valves would be incompetent.[2] There are many reports in the literature regarding the competency of the ileocecal valve in post-mortem specimens[5-7]; however, there are only scattered reports of reflux pressures measured in vivo.[7] The fact that the ileocecal valve is a physiologic valve which prevents reflux from the colon to the ileum appears well established. For this reason, the ileocecal valve has been suggested as a substitute for the cardiac sphincter in conditions when resection of the cardia is necessary and when some mechanism is needed to prevent reflux esophagitis following surgery. The substitution of the ileocecal valve for the cardiac sphincter has been carried out in dogs and has been reported.[4] In one series of 16 dogs with transplantation of the ileocecal valve, the reflux resistance of the valves was reported as 50 cm. H_2O pressure in specimens examined at autopsy.

The material presented in this paper deals with the adequacy of the ileocecal valve as a mechanism to prevent regurgitation. It is concerned with a comparison of pressures required to cause reflux from the colon to the ileum and from the stomach to the esophagus in dogs as well as with the pressures required to cause reflux from the colon to the ileum in patients examined at fluoroscopy.

METHODS

Under barbiturate anesthesia, laparotomies were performed on 10 dogs and the competency of the ileocecal valve ascertained. The animals were sacrificed to determine the competency of the valve at intervals up to 24 hours following

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death. Competency of the valve was measured by injecting water into the ascending colon which was occluded by a clamp 10 to 12 cm. distal to the ileocecal valve. Pressures were measured at the time of reflux into the ileum. Through a small incision in the terminal ileum, the end point, when regurgitation occurred, was seen easily. Pressures at which reflux occurred were recorded in vivo in 2 dogs whose ileocecal valves had been transplanted between the esophagus and stomach.

In 10 dogs the cardiac sphincter was studied. The stomach was occluded 6 to 8 cm. distal to the cardia. Water was injected into the stomach until the pressure overcame the resistance of the cardiac sphincter and caused reflux into the esophagus. Pressure readings were recorded at the time of reflux. All pressures were recorded in centimeters of water as measured by a spinal water manometer.

The ileocecal valve was studied in 25 patients having barium enemas. By means of a Y tube, a U tube water manometer was connected to the barium enema tubing. Pressures were recorded in the rectum at the time of reflux of barium from the cecum to the ileum. At the time of recording the pressures, the barium source was excluded from the pressure circuit to permit more accurate pressure readings.

RESULTS

In dogs, the competency of the ileocecal valve in vivo varied from complete incompetence to competency at 28 cm. H_2O pressure, with an average of 13.4 cm. H_2O pressure (Table I). Two dogs in which the ileocecal valve was substituted for the cardiac sphincter were found to reflux at 13 and 15 cm. H_2O pressure,

TABLE I. SERIAL REFLUX PRESSURES ON THE ILEOCECAL VALVES OF DOGS (CM. H_2O)

DOG NUMBER	PRESSURE IN VIVO	PRESSURE AT DEATH	PRESSURE 1 HOUR POST MORTEM	PRESSURE 6 HOURS POST MORTEM	PRESSURE 24 HOURS POST MORTEM
1	3 to 5	3 to 5	0	0	0
2	28	17	0	17	17
3	0	0	0	28	17
4	12	12	14	20	20
5	10	0	0	-	36
6	15	12	3	23	36
7	10	-	-	-	-
8	14	6	6	6	6
9	26	0	0	22	-
10	15	15	15	23	0
Average	13.4			Average	19

respectively. The resistance to reflux of the valve after death was found to be higher than in life in over 50 per cent of the dogs examined. The average after death was 19 cm. H_2O pressure as compared with 13.4 cm. in vivo.

The resistance of the cardiac sphincter to reflux varied between 0 and 60 cm. H_2O pressure with an average competency of 36 cm. (Table II).

TABLE II. REFLUX PRESSURES ON THE CARDIAC SPHINCTER OF DOGS

DOG NUMBER	REFLUX PRESSURE (CM. H_2O)
1	60 (no reflux)
2	40
3	40
4	26
5	56
6	48
7	16
8	0
9	30 (Ileocecal valve was incompetent completely)
10	48 (Ileocecal valve was competent to 10 cm. H_2O pressure)
Average	36.4

Measurements of the human ileocecal valve to reflux revealed a wide variation. Readings ranging from 10 to 97 cm. H_2O pressure were obtained with an average of 36.6 cm. H_2O pressure (Table III). Five of the valves tested had a reflux pressure of 20 cm. H_2O or lower. In one of the valves no reflux occurred with a pressure above 90 cm. H_2O.

TABLE III. PRESSURES IN THE RECTUM AT TIME OF REFLUX OF BARIUM FROM CECUM TO ILEUM

PATIENT NUMBER	PRESSURE AT TIME OF REFLUX (CM. H_2O)
1	24
2	50
3	10
4	36
5	42
6	50
7	42
8	20
9	*
10	21
11	97 (No reflux)
12	10
13	30
14	20
15	38
16	24
17	60
18	54
19	18
20	39
21	17
22	39
23	38
24	58
25	24
26	36
27	28

*Results not reliable due to technical difficulty.

DISCUSSION

In this study the average reflux resistance of the ileocecal valve of the dog was one-third that of the cardiac sphincter. We were unable to confirm the high and consistent degree of competency of the ileocecal valve of the dog reported in work previously quoted.[4] Post-mortem pressure studies on the ileocecal valve are unreliable, since they were found to be higher than in vivo valves.

It was thought that the method used to measure the reflux pressure in the human ileocecal valve during a barium enema might be inaccurate since pressure readings in the rectum conceivably were different from pressures in the cecum. Simultaneous rectal and cecal pressures were measured in dogs and were found to be identical at lower pressures. At pressures above 25 cm. the rectal pressure was less than 10 per cent higher than the cecal pressure.

Twenty per cent of the patients tested had reflux into the ileum at pressures of 20 cm. or below, 36 per cent had reflux at 25 cm. or below, 84 per cent had reflux at 50 cm. or below, and 96 per cent had reflux at 90 cm. or below. One individual had an ileocecal valve which was nearly completely incompetent, refluxing at 10 cm. H_2O pressure. Thus, it would appear that there is a wide physiologic variation in the ability of the valve to prevent reflux and that a significant portion of the population has a relatively incompetent ileocecal valve.

SUMMARY AND CONCLUSIONS

1. The degree of reflux resistance of the ileocecal valve and cardiac sphincter of the dog was determined and compared.

2. The average reflux resistance of the ileocecal valve was only one-third that of the cardiac sphincter. The transplanted ileocecal valve of the dog refluxed at the same range of pressure as the normal ileocecal valve.

3. Post-mortem pressure studies on the ileocecal valve appear to be unreliable.

4. The reflux pressures of the human ileocecal valve were measured indirectly by recording pressures in the rectum at the time of reflux of barium into the ileum.

5. A wide variation in the reflux resistance of the human ileocecal valve was found. This observation casts some doubt upon the universal adequacy of the ileocecal valve to prevent reflux. As a result of these studies, it is recommended that a preoperative evaluation of the competency of the ileocecal valve is indicated before substitution of this structure for the cardiac sphincter.

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FLUORESCEIN STRING TEST FOR LOCALIZATION OF UPPER GASTROINTESTINAL HEMORRHAGE

A Preliminary Report

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A NEED exists for a supplemental method of localizing the site of upper gastrointestinal hemorrhage. At present the clinician is unable to localize the site of bleeding in approximately 15 per cent of the cases.[1-4] The management of gastrointestinal hemorrhage is in itself a major one but certainly becomes compounded when the diagnosis and site of bleeding are unknown. The treatment then becomes empirical, the morbidity increases, and mortality is always a constant threat. In an effort to reduce the percentage of cases in which the site of bleeding is unknown, a modification of the string test has been developed and utilized.

The following materials are essential in order to perform the examination:

1. String (A thin $\frac{1}{32}$ inch gauze umbilical tape†).—A radiopaque marker is imprinted longitudinally into the string for a distance of 7 feet, and the string is cross-marked with the same material at one inch intervals (Fig. 1). A small 2 Gm. shot is attached to the end of the string to facilitate swallowing and passage through the pylorus.

2. Fluorescein (5 Per Cent) Processed With Sodium Bicarbonate.—This sterile solution is not toxic and can be given in comparative amounts as normal saline without difficulty.‡

3. An ultraviolet light or small Mineralight.§

The string is moistened with water and usually swallowed without difficulty by the patient. A flat film of the upper abdomen is obtained 2 to 3 hours later to determine the string's location. It is desirable to pass the end of the string to at least 2 feet beyond the ligament of Treitz. It is easy to detect the course and progression of the string by noting the radiopaque markers and their relationship to the pylorus.

When it is apparent that the patient is having active gastrointestinal bleeding, that is, a fall in hemoglobin, hematocrit, red blood cell count, and clinical signs of hemorrhage, 20 c.c. of fluorescein is injected into an antecubital vein. After a lapse of 5 minutes the string is removed. The string is examined first for evidence of gross blood and then taken to a darkened room and examined against a dark background with an ultraviolet light. Examination of the string may disclose three possibilities.

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†Supplied by Johnson and Johnson Company, New Brunswick, N. J.

‡Supplied by the C. F. Kirk Company, New York City.

§Supplied by Ultra-Violet Products, Inc., South Pasadena, Calif.

A. The string may contain no blood or fluorescein. This indicates that there is no active or recent bleeding in the area passed by the string or that the string is above the point of hemorrhage.

B. The string may contain only blood and no fluorescein. This indicates that active bleeding is not occurring at the moment of the test and that bleeding had occurred at some time in the past in that area.

C. The string may contain both blood and the fluorescein dye. This indicates that active bleeding is occurring and the site of the dye indicates the point of origin of the hemorrhage. This is determined by matching the place where dye occurs on the string with its comparable location on the x-ray film. Due to the typical curvature of the string in the region of the duodenal C loop, accurate anatomic localization of the bleeding point is readily obtained. If the appearance of the dye on the string seems equivocal, then the fluorescein can be made strikingly apparent by immersing the string in a trough of water and examining it under an ultraviolet light.

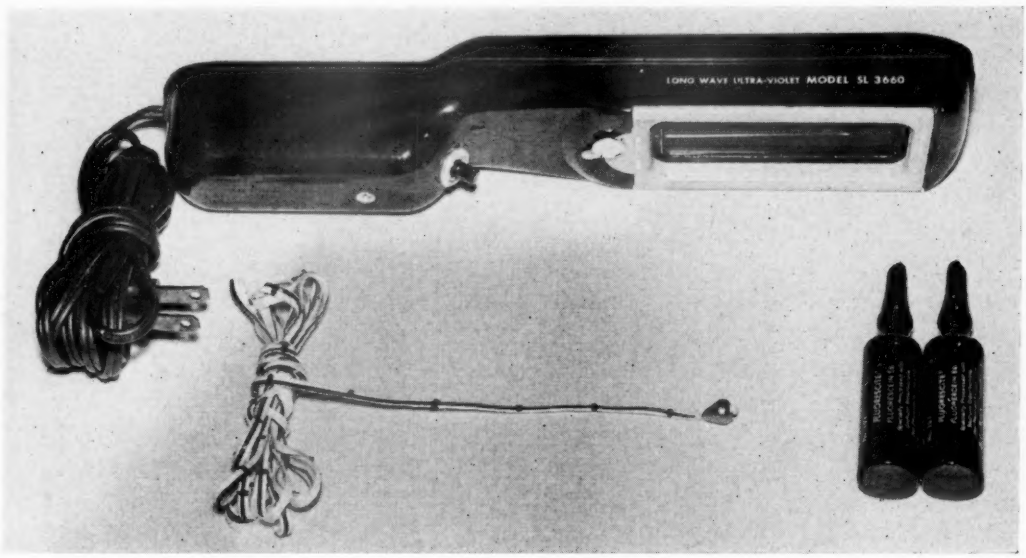

Fig. 1.—This photograph depicts the equipment needed to perform the fluorescein string test. These include an ultraviolet light, sterile fluorescein solution, and a radiopaque marked string as shown.

To date this test has been used with satisfactory results on patients having upper gastrointestinal hemorrhage from numerous different sources. Bleeding from hiatal hernia, linitis plastica, pre- and postpyloric ulcers, a marginal ulcer, esophageal varices, and even a duodenal carcinoma have been localized using the fluorescein string test. Further clinical application of this test is thought advisable.

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URINARY DIVERSION

Metabolic Alterations Associated With Use of Isolated Ileal Segments

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THE need for a suitable method of urinary diversion in the absence of a normally functioning urinary bladder has long been recognized. Consequently, many ingenious operations have been devised, but despite these efforts many problems remain. Ureteral obstruction, urinary tract infection, hydronephrosis, and pyelonephritis are frequent complications and hyperchloremic acidosis is not uncommon. Until a few years ago cutaneous ureterostomy and ureterosigmoid anastomosis, despite their shortcomings, were generally considered the methods of choice. With the advent of pelvic exenteration came the necessity of carrying out urinary diversion in the absence of a pelvic colon. The evaluation of other procedures, particularly the wet colostomy,[4, 5] ileocecal segment,[11, 12] and ileal bladder,[2, 3] followed.

Bricker,[3] in 1950, published the first modern evaluation of the use of the isolated ileal segment and his initial enthusiasm has been justified by subsequent experience. During the past few years the procedure has been more generally applied and the reports of Cordonnier,[7] Wells,[17] Pyrah,[13] Wawro[16] and others substantiate its value under various circumstances.

From data now at hand it is apparent that the incidence of renal infection, and subsequent renal damage, is much less than with the older diversional methods. In addition, the metabolic imbalance (hyperchloremic acidosis) associated with ureterosigmoidostomy has been almost eliminated, at least at the clinical level. It is with this aspect that we are particularly interested, but a review of our general experience with the method will be presented.

MATERIAL

Urinary diversion by means of anastomosis of the ureters to an isolated segment of terminal ileum has been performed in 20 patients at the Veterans Administration Research Hospital during the past 4 years. Previous experience with the operation elsewhere had satisfied us that the procedure possessed considerable merit.

The indication for bladder substitution in each of our patients has been advanced malignant disease. Fifteen of the patients had extensive invasive cancer of the urinary bladder, 4 had carcinoma of the rectum or rectosigmoid with bladder invasion, and one had a rhabdomyosarcoma involving the

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bladder and prostate. The procedure is also well suited to nonmalignant indications for urinary diversion as noted in the reports of others. In fact, the longer the life expectancy of the individual, the greater is the indication for this method of urinary diversion, since late complications have been infrequent. In view of the nature of our material long-term survival is not to be anticipated in more than a few patients; indeed, the majority have already died of cancer.

The nature of the associated operation is indicated in Table I. All were single stage procedures.

TABLE I

Ileal bladder only; palliative	4
Ileal bladder and simple cystectomy	2
Ileal bladder and cystectomy with prostatoseminovesiculectomy and pelvic lymphadenectomy	9
Ileal bladder and pelvic exenteration	5

The operative technique which we utilize has been recorded and will not be repeated here.[14] It is, with minor exceptions, the same as the procedure initially described by Bricker; in fact, our initial experience was acquired through his former associates at the Ellis Fischel State Cancer Hospital, Columbia, Missouri.

MORBIDITY AND MORTALITY

In all but a few of the 20 patients the construction of the ileal bladder was accompanied by an extensive pelvic dissection. In 14 of the 20 patients the urinary bladder, paravesical tissues, prostate, and seminal vesicles were removed, accompanied by an extensive bilateral pelvic lymph-node dissection with resection of the hypogastric vessels and their pelvic tributaries; in 5 of the 14 the pelvic colon was also removed.

Despite the extent of the procedure there has been but one operative death (herein defined as death from any cause within 30 days of operation), and this was due to pulmonary embolism. There has been no mortality associated with the construction of the ileal bladder per se, nor have there been such serious sequelae as urinary or fecal fistula, intestinal obstruction, or ileostomy stenosis. Adynamic ileus has occurred with a somewhat greater frequency than one might anticipate following major abdominal surgery.

BLOOD CHEMISTRY

Frequent determinations of blood urea nitrogen, carbon dioxide combining power, and serum sodium, potassium, and chloride were performed in practically all patients in the preoperative period, the early postoperative period, and at varying intervals thereafter. These data, omitting the 2 most recent patients because of inadequate length of follow-up, are presented in Table II. The laboratory data immediately prior to surgery are listed under the "preoperative" heading. The "early postoperative" heading includes the first 30 days after surgery, while the "late postoperative" heading refers to determinations done after 30 days. The whole number in the last 2 categories represents the trend for the determinations during the specified period

TABLE II

PATIENT NUMBER	BLOOD UREA NITROGEN			CARBON DIOXIDE			CHLORIDES			SODIUM			POTASSIUM		
	PRE-OPERATIVE	EARLY POSTOPERATIVE	LATE POSTOPERATIVE	PRE-OPERATIVE	EARLY POSTOPERATIVE	LATE POSTOPERATIVE	PRE-OPERATIVE	EARLY POSTOPERATIVE	LATE POSTOPERATIVE	PRE-OPERATIVE	EARLY POSTOPERATIVE	LATE POSTOPERATIVE	PRE-OPERATIVE	EARLY POSTOPERATIVE	LATE POSTOPERATIVE
1.	19	29 15/44	17 14/121	29	24 21/30	24 11/26	107	99 90/103	107 102/117		125				5.9
2.	17	20 19/22	17 15/20	27	26 23/30	25 24/26	101	105 101/109	104 100/106		136				5.2 4.7/5.6
3.	8	12		23	28		109	103			138			5.8	
4.	21	18 16/23	17 14/22	29	26 24/27	25 22/28	114	114 114/116	108 105/111		137	142 137/146	4.5	4.1	5.0 4.6/5.4
5.	17	21 13/31	17 12/23	26	28 27/31	21	114	98 97/99	97 91/103	136	134	132 128/135	5.7	5.6 5.3/5.8	5.8
6.	17	22 21/22	21 15/28	22	24 22/25	27 27/28	101	108 104/112	111 110/116		128	145 137/150			4.8 4.5/5.3
7.	13	25 14/65	30 22/69	26	24 17/30	21 10/26	106	104 85/108	112 97/122	140	135 119/144	136 131/145	6.0	4.5 3.6/5.8	5.3 3.6/5.9
8.	14	16 12/21	11 8/16	27	29 27/32	27 24/30	100	102 94/108	103 97/109	135	136 134/138	140 135/145	4.6	4.8 4.7/5.0	4.6 4.5/4.7
9.	13	18 15/22		24	26 23/29		106	106 100/111		135	138		5	5	
10.	16	14	11 10/11	27	30 27/24	27 22/30	103	99 91/107	96 96/96		130	138 136/140	5.2	4 3.5/4.0	4.6 4.0/5.2
11.	14	25 19/27	22 19/43	27	24 23/30	23 20/29	112	106 98/108	107 106/114	130	137	145 139/157	4.4	4.8 4.5/5.7	4.2 4.0/4.8
12.	49	60 33/85	31	28	24 20/29	20	113	102 96/113	99	140	138 135/139		4.0	4.8 4.0/5.8	5.8
13.	17	21 16/27	14 11/22		27 24/30	26 24/28		105 97/113	104 101/109						
14.	11	18 13/26	26 21/49		26 19/28	18 14/22		98 92/104	102 98/113	140	140 139/142	132 121/135		4.5 4.4/5.7	7.0 6.4/7.6
15.	21	30 17/50	45 18/125	26	16 14/23	20 11/23	101	106 102/113	100 86/118	136	136 125/140	140 123/148	4.8	4.9 3.8/6.0	3.8 2.6/5.6
16.		13 13/14			25 24/26			106 104/111		138	138 130/140			5.0 4.0/5.5	
17.	8	26 25/55	40 38/58		26 18/33	17		103 98/106	105		135 125/146				5.0 3.5/6.0
18.	19	20 15/21	16 13/20	24	27	27	105	91	109		132	142		4.4	4.3

while the fraction represents the minimum and maximum values obtained during the period. An over-all biochemical evaluation is thus presented, rather than the values existing at an arbitrary point, such as 3 months or 6 months.

The majority of these patients had already sustained at least a moderate degree of renal damage, usually on the basis of ureterovesical obstruction, prior to urinary diversion. In only 5 of the 18 patients were preoperative pyelograms completely normal and one of these had had a previous nephrectomy.

Blood urea nitrogen values in the early postoperative period (30 days) are often transiently elevated. A slight increase is noted in the majority of patients and significant (above 40 mg. per cent) although transient elevations occurred in 5 of the 18. The trend during the first postoperative month was only slightly higher than the preoperative values.

Six of the 18 patients, including 4 of those with early postoperative increase showed sporadic elevation of the blood urea nitrogen during the late postoperative period, although on several occasions this was probably attributable to factors other than renal function per se. The trend in the majority remained relatively normal considering the preoperative renal status of most of the patients.

Significant decrease in carbon dioxide combining power (< 17 mEq./L.) occurred in 4 of the 18 patients. The most marked changes occurred just before death from advanced cancer in 2 patients and unrelated peritonitis in a third and were associated with elevated chloride levels in each. In addition, increased levels of urea nitrogen were present in all 4 with marked elevations in 2.

Elevation of serum chloride values above the generally accepted level of normal (105 mEq./L.) occurred on at least one occasion in 16 of the 18 patients. This is in marked contrast with the findings of others who have ordinarily reported chloride values to be within normal limits. Wells[17] presented the chemical values in a collected series of 201 cases. Many of these values were above levels usually considered normal but he concludes "that the blood chemistry is virtually unchanged by ileal ureterostomy." He continues, "If we consider only the postoperative results it will be seen that a considerable number fall outside the normal limits but here we have also the preoperative figures for comparison and, considering the patients as a group, the gains balance the losses very neatly." Cordonnier[7] simply states that "hyperchloremic acidosis has produced no problem either early or late." Baker and Graf[1] state "there has not been an instance of electrolyte disturbance" in a group of 20 patients. They do not define the term "electrolyte disturbance" and no laboratory data are included.

There would seem to be a need for a more precise definition of the term "hyperchloremic acidosis." For example, Ferris and Odel[10] are frequently quoted as finding elevation of the serum chlorides in 79 per cent of 141 patients with bilateral ureterosigmoidostomy. However, they considered any value over 103 mEq./L. (on one or more of multiple examinations) as being

abnormally high. Only 55 per cent had a value of 107 mEq./L. or over, and only 31 per cent had values of more than 110 mEq./L. A similar situation exists for their evaluation of carbon dioxide combining power, in that any value below 23 mEq./L. was considered abnormal. Bricker[3] states "in only two patients has an elevated serum chloride been found at any time after operation." In an earlier article[8] in which data are presented on 9 patients (6 months or more after ureteroileostomy), 6 of the 9 had chloride values of 107 mEq./L. or more and 3 of these were 110 mEq./L. or more but the carbon dioxide combining power was within normal limits in each instance. In contrast, Wilson reports a case under the title "hyperchloremic acidosis" with a carbon dioxide combining power of 12.5 mEq./L. and a serum chloride of only 107.5 mEq./L. The term "hyperchloremic acidosis" is apparently interpreted differently by the various authors. If the term is used in reference only to those patients with clinical manifestations, the incidence will certainly be much less than if one adheres strictly to so-called normal laboratory values without consideration of the variations[9] which occur in normal individuals. One may conclude, from the experience of others as well as our own, that with rare exceptions hyperchloremic acidosis, as a clinical entity rather than a laboratory entity, does not occur.

Our data is presented in somewhat abbreviated form in Table II. It is emphasized that 4 patients had preoperative chloride levels over 110 mEq./L. and an additional 4 of over 105 mEq./L.

The trend during the postoperative period was much the same as the preoperative status, with practically all patients showing values below 110 mEq./L. On the other hand there were numerous random or sporadic determinations which showed a more marked elevation (Table II).

The frequency of hyperchloremic acidosis therefore depends upon the definition of the term. From a study of our patients, 4 of the 18 had chloride values of 110 mEq./L. or more with concomitant carbon dioxide values of 15 mEq./L. or less. Only one had clinical manifestations attributable thereto. Three of the 4 were terminal (from other causes, as previously noted) and died within a few days. In the 2 patients who died of cancer, no attempt was made to maintain adequate fluid and electrolyte balance; oral intake was obviously inadequate. The third patient had a stormy course following surgery for a diffuse peritonitis, the result of colostomy perforation during an unskilled irrigation, with parenteral nutrition maintained over a long period of time. In these 3 patients there were therefore factors other than renal which in themselves could lead to metabolic imbalance. Nitrogen retention, as indicated by blood urea nitrogen studies, was present in all 4, and to a marked degree (121 and 125) in 2 of the 4.

We do not believe the hyperchloremic acidosis played a role in the clinical course of these 3 patients or was responsible in any way for their death. In all 3 it occurred as a terminal manifestation and existed for only a short time.

We have had one patient, however, with a full-blown picture of hyperchloremic acidosis, chemically and clinically.

Patient 7.—A 59-year-old white man had first noticed urinary frequency and dysuria in November, 1954. A diagnosis of bladder cancer was established at another hospital in April, 1955, at which time the tumor was treated through a suprapubic transvesical approach. Persistent disease was recognized in July, 1955, and the patient was referred to this hospital. Preoperative intravenous pyelograms revealed a nonfunctioning kidney on the right and a severe hydronephrosis on the left.

After extensive preoperative evaluation, total cystectomy with prostatoseminovesiculectomy and bilateral pelvic lymphadenectomy was carried out (July 19, 1955). The right ureter was markedly dilated and its contents were grossly purulent. The left was moderately dilated but contained clear urine. Right nephrectomy was considered but it was decided to implant both ureters into the isolated ileal segment.

In mid-August the patient complained of mild left costovertebral discomfort associated with a slight temperature elevation. These responded promptly to antibiotic therapy. The fever and pain recurred on Oct. 5, 1955, persisted for several days, then gradually disappeared on antibiotic therapy. During this period marked chemical changes occurred and were associated with the classic clinical picture of hyperchloremic acidosis (Table III).

TABLE III

DATE	BLOOD UREA NITROGEN	CO_2	Cl_2	Na	K
July 12, 1955	13	25	105	140	6.0
July 19, 1955	Surgery				
July 20, 1955	26	25	95	119	
July 23, 1955	63		109	137	
July 29, 1955	52	30	100	144	4.3
Aug. 4, 1955	18	27	95	135	4.2
Aug. 19, 1955	22	18	106	141	5.8
Aug. 27, 1955	24	15	113	133	5.7
Sept. 9, 1955	26	21	110		
Sept. 20, 1955	30	26	109		
Oct. 9, 1955	59	16	110		
Oct. 17, 1955	54	10	112		
Oct. 19, 1955	47	10	122	145	
Oct. 20, 1955	43	15	115	140	5.8
Oct. 23, 1955	35	23	113		
Oct. 29, 1955	30	25	109		

The patient became lethargic, complained of thirst, weakness, fatigue, severe anorexia, and occasional vomiting. His chemical status was followed daily until the CO_2 reached a level of 10 mEq./L. with a chloride of 122 mEq./L.; treatment was withheld during this period in order to observe the magnitude of the chemical change. When these levels (Oct. 19, 1955) were reached sodium bicarbonate was administered, 2 Gm. four times daily, without other change in management. The response was dramatic; he brightened up considerably and became interested again in his environment, his appetite improved, and he regained strength rapidly. His chemical findings paralleled his clinical improvement (Table III). After a few days the dosage of sodium bicarbonate was decreased to 4 Gm. per day; improvement continued and the bicarbonate administration was subsequently discontinued without further difficulty. Although occasional abnormal chemical values were obtained during the next few months they did not parallel those associated with the episode of pyelonephritis and the administration of sodium bicarbonate was never again necessary.

With few exceptions serum sodium values were within normal limits and the variations which were noted did not correlate with other electrolyte abnormalities.

Hypokalemia has been incriminated in the pathogenesis of the hyperchloremic acidosis of ureterosigmoidostomy.[15] Serum potassium levels below

4.5 mEq./L. were obtained on 13 occasions in 10 patients, including the patient with hyperchloremic acidosis but not at the time the hyperchloremic acidosis existed. The low potassium values were frequently associated with moderate depression of serum chlorides and elevation of carbon dioxide combining power but not with hyperchloremic acidosis.

Serum potassium values above 5.5 mEq./L. were obtained on 17 occasions in 10 patients. The CO_2 was concomitantly abnormal (< 17 mEq./L.) in 4 of the 17 examinations and the chlorides abnormal (> 105 mEq./L.) in 3 of the 17; the CO_2 was abnormal also in 2 of these 3. The potassium values were 5.7 mEq./L. on the 2 occasions when carbon dioxide depression and chloride excess existed concomitantly. The blood urea nitrogen was greater than 30 mg. per cent in 7 of the 17 determinations and correlates better with increased serum potassium values than do the carbon dioxide or chloride values.

A chemical hyperchloremic acidosis was more frequently associated with hyperkalemia than hypokalemia. Although this may represent a fortuitous association, it may also have been mediated through a coexisting renal insufficiency. There is little to suggest an etiologic association between hyperchloremic acidosis and either hypo- or hyperkalemia. In these patients it must be recalled that many other factors exist, especially in the early postoperative period, which may influence potassium balance.

PYELONEPHRITIS

One of the most frequent sequelae of ureterosigmoid anastomosis is infection in the form of pyelitis or more often pyelonephritis. This complication may also follow ureteroileal anastomosis but is considerably less frequent. Bricker[3] reports 12 patients with pyelonephritis of 65 patients followed for over 6 months, an incidence of 18 per cent. Wells,[17] in a collected series of patients with ileal bladders, recorded 11 instances in 156 patients (7 per cent) but the duration of follow-up is not stated.

We have clinical evidence of pyelonephritis in 2 patients, perhaps 3. Patient 7 is described in detail. Patient 11 was hospitalized elsewhere a few months after discharge because he had developed severe pelvic pain secondary to persistent tumor. Cordotomy was performed and paraplegia followed. Several months later, a few weeks prior to death, he developed chills and fever, otherwise unexplained, which was attributed to pyelonephritis. Patient 13 had one episode characterized by chills, fever, and flank pain. This responded readily to treatment and there had been no recurrence 6 months later. If one considers the related circumstances, the infection in the first 2 patients is perhaps understandable; in the third, however, there is no explanation other than to attribute it to the method of urinary diversion per se, even though intravenous pyelograms were normal.

PYELOGRAPHIC STUDY

Pre- and postoperative intravenous pyelograms were obtained in practically all patients. These have been classified by Bricker's method on the basis of individual renal units as follows:

Grade 0—Normal intravenous pyelogram
Grade 1—Minimal hydronephrosis
Grade 2—Definite hydronephrosis
Grade 3—Massive hydronephrosis
Grade 4—Nonfunctioning kidney (We have included those with insufficient dye excretion for adequate interpretation.)

The results of intravenous pyelography 3 months postoperative are presented in Table IV. One patient had had a nephrectomy, leaving 35 renal units for evaluation; 2 patients are too recent for evaluation. Three patients did not have an intravenous pyelogram during this period.

TABLE IV. INTRAVENOUS PYELOGRAPHY

	PREOPERATIVE	3 MONTHS POSTOPERATIVE
Grade 0	17	14
Grade 1	2	5
Grade 2	3	5
Grade 3	5	0
Grade 4	6	5
No intravenous pyelography	2	6

Only 15 renal units were available for follow-up study 6 months or more after surgery. Of the 15, 10 were completely normal and 3 showed minimal-to-moderate hydronephrosis. There were 2 nonfunctioning units, both of which had been nonfunctioning prior to surgery.

In addition to intravenous pyelograms we have performed retrograde ileopyelograms on 16 of the 18 patients. A catheter is passed 4 to 6 cm. through a small opening in the tip of a Hygeia-type bottle nipple. The nipple, with catheter protruding, is then inserted into the ileostomy, and with gentle pressure a radiopaque substance is injected, preferably under fluoroscopic control. The nipple prevents escape of the solution from the isolated segment and facilitates reflux of dye up the ureters. Such examination demonstrates that the ureterointestinal anastomosis (Cordonnier type) permits ready reflux of the injected material, and retrograde pyelograms comparable to those following ureteral catheterization can be obtained in most patients. In an occasional instance it should prove to be a valuable addition to the study of the patient with an ileal bladder just as retrograde pyelograms are occasionally indicated in patients with normal bladders.

SUMMARY

Urinary diversion by means of ureteroileostomy has been carried out in 20 patients with advanced malignant disease of pelvic origin. In spite of the extent of surgery (including multiple visceral resection and lymph-node dissection in most instances) accompanying the urinary diversion there has been only one operative death and this was due to pulmonary embolism. There have been no deaths due to the construction of the ileal bladder per se and no serious sequelae.

Pyelographic and chemical studies in these patients have been satisfactory for the most part but some metabolic imbalance has been noted and one case of outright hyperchloremic acidosis is recorded.

Retrograde ileopyelography is suggested as a valuable adjunct in the study of the occasional patient with an ileal bladder.

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POSTSURGICAL ANURIA: AN EXPERIMENTAL STUDY OF FLUID AND ELECTROLYTE CHANGES

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THE purpose of this study was to measure and evaluate the shifts of fluid and electrolytes that occur in acute and total anuria following surgical procedures. Methods employed included: (1) serial determinations of plasma volume and the space of distribution of sucrose and inulin, (2) determination of the changes in concentration of plasma electrolytes, (3) estimation of intracellular (muscle) water and electrolytes by serial biopsy and tissue analysis, (4) metabolic balance studies, and (5) estimation of total body potassium by means of radioactive potassium dilution studies.

METHODS

Mongrel dogs, ranging from 15 to 21 Kg. in weight, maintained in an air-conditioned kennel and fed Purina Fox Chow were used.

Plasma sodium, potassium, chloride, phosphate, and carbon dioxide contents were determined by methods previously described.[16] Magnesium was determined by the method of Simonsen and associates[22] and blood urea nitrogen by the method of Van Slyke and Cullen.[26] pH was measured in whole blood in a Cambridge pH meter at 37° C.

In the control studies inulin spaces were determined by a constant infusion method.[21] To equalize the extrarenal loss of inulin in both control and anuric animals the "zero time" in the single injection technique was plotted at a point of elapsed time equal to the equilibration time of the constant infusion technique. In 2 experiments sucrose was employed instead of inulin. The methods used were otherwise the same.

We realize that no technique including inulin and sucrose dilution corresponds fully with the actual "extracellular space," but we believe that these substances can be used as a relative index of change in this fluid compartment, especially when each animal serves as its own control. For the sake of convenience we will frequently refer to extracellular fluid (ECF). It is understood that throughout the paper we are referring only to that space measured by inulin or sucrose.

Plasma volume was measured by the use of Evans blue dye (T1824).[8]

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Anuria was produced in the animals by ligatures placed on the ureters at the level of the brim of the pelvis. This created a dead space in the renal pelvis and ureters. Total fluid in this space in both kidneys was aspirated in 3 dogs and was found to vary between 12 and 40 c.c. after the ligatures had been in place for 72 hours. Inulin content in this fluid after the usual infusion of inulin was four times the plasma concentration. Thus the maximum error introduced by the dead space was 160 c.c. Since this is within the limit of error of the sucrose or inulin method, this dead space was disregarded in our final calculations. Electrolytes in the dead space were also determined in these animals and were likewise found to be negligible compared to total body content.

A calculation of the intracellular electrolytes of muscle was obtained by biopsy of the sartorius or rectus muscle in each animal. After all surrounding fat and fascia were cleared away, a large clamp was placed above and one below the site of biopsy. These were closed at the instant that the blood sample for serum electrolytes was drawn. By this method relatively little contamination of the specimen by hemorrhage occurred. The specimen was transferred to a moisture-tight container and minced into a fine pulp. Water content, sodium, potassium, chloride, and inulin or sucrose content were determined.[17] The concentration of muscle electrolytes was calculated in terms of milliequivalents per kilogram of water of fat-free muscle. A Donnan factor of 0.95 was used for plasma cations and of 1.05 for anions. Serum solids were estimated at 6 per cent. No allowance was made for extracellular fluid solids.

Control studies in each animal consisted of a determination of plasma sodium, potassium, chloride, carbon dioxide, and pH. In several animals plasma magnesium, phosphate, and blood urea nitrogen were also measured. Plasma volume, inulin or sucrose space, muscle water, and electrolytes were also determined. From several hours to a week after the control studies, the dogs' ureters were ligated transabdominally under general anesthesia. Blood loss was minimal. Following operation the dogs were kept in metabolic cages and a daily record of intake and output and the dogs' weights were recorded. Fluid replacement varied somewhat, but in most dogs an attempt was made to replace half the daily weight loss with 5 per cent dextrose in water. In 3 dogs a balance study of chloride was done. Seventy-two hours after the onset of anuria all of the previous space studies, muscle and plasma electrolytes and pH, were repeated. Dog 3b differed from the others in that fluids by mouth were unrestricted during anuria. In Dog 43 the ligatures were removed from the ureters and a second control study was done 5 weeks after the first experiment.

Total available body potassium was determined in the animals in the control and anuric phases with radioactive potassium.

Only local anesthesia was used throughout both the control and anuria studies, except during ligature of the ureters. In no instance was muscle infiltrated.

RESULTS

Table I summarizes the changes in concentration of the various constituents of the plasma following approximately 72 hours of anuria. Comparing the anuric animals to the controls, it is noted that there was usually a slight drop in plasma sodium and a greater drop in plasma chloride and carbon dioxide. Plasma potassium, phosphate, magnesium, and blood urea nitrogen were definitely increased. The values of blood pH and hematocrit decreased. Figs. 1-3 are scattergrams illustrating the direction of change in concentration of sodium, potassium, and chloride as a percentage of the control plotted over the entire period of anuria.

TABLE I. CHANGES IN PLASMA ELECTROLYTES AND OTHER VALUES BEFORE AND AFTER ANURIA

DOG NUMBER	CONTROL									ANURIC								
	Na	K	Cl	CO_2	Mg	PO_4	pH	BUN	HCT.	Na	K	Cl	CO_2	Mg	PO_4	pH	BUN	HCT.
3b	144	3.7	112	20	1.5	0.9	7.39	12.5	48	131	5.3	101	10.9	2.4	3.5	7.21	---	28
117	140	3.4	117	19	0.7	1.5	7.31	12.5	42	138	9.7	96.4	17	2.6	4.9	7.18	194	31
46	139	3.4	112	20	--	1.0	7.36	---	35	144	7.6	99.8	12	--	9.9	7.21	---	41
43a	143	3.0	108	17	--	1.1	7.40	---	34	139	6.0	103	16	--	3.0	7.26	---	38
43b	137	2.9	110	19	--	1.0	---	---	46	---	--	----	--	--	--	---	---	--
99	147	3.6	116	27	--		---	---	45	129	7.0	90.8	22	--	--	7.14	---	--
112	132	3.1	110	19	1.0	0.5	7.31	11.0	40	132	7.3	99.5	14	3.3	5.2	7.08	163	29
139	135	3.8	113	23	1.3	1.0	7.25	17.9	34	135	7.5	96.8	16	2.4	7.0	7.27	200	29
113	146	2.3	109	26	--	1.0	7.34	12.7	47	133	4.8	96.7	20	--	5.2	7.35	144	40

There was a consistent rise of potassium, magnesium, phosphate, and blood urea nitrogen in all animals and a consistent fall in chloride, carbon dioxide, and pH. Hematocrit fell in 5 of 7 animals and sodium fell somewhat in 5 of 8 animals, remaining at about the same level in the other three. Electrolytes are expressed in milliequivalents per liter, except phosphate which is expressed in millimoles per liter. Blood urea nitrogen is in milligrams per cent and hematocrit in millimeters.

TABLE II. CHANGES IN EXTRACELLULAR FLUID AND TOTAL EXTRACELLULAR ELECTROLYTES

DOG NUMBER	CONTROL							ANURIC						
	P.V.	ECF	Na	K	Cl	Mg	PO_4	P.V.	ECF	Na	K	Cl	Mg	PO_4
3b*	1,040	4,530	627	16.1	527	6.53	8.00	----	5,200	646	26.2	551	11.7	32.8
117	750	4,800	644	16.0	539	3.28	10.57	----	4,000	534	36.9	405	9.9	35.8
46	1,007	4,000	537	13.4	465	---	7.18	844	3,270	454	24.0	338	---	57.5
43	2,150	4,950	686	14.5	549	---	10.10	1,273	3,737	512	21.6	399	---	20.0
43	1,040	5,200	679	14.7	595	---	8.40	----	----	---	---	---	---	---
112	1,440	6,400	812	22.3	641	6.16	7.10	1,120	4,850	616	34.1	502	15.4	43.2
139	2,200	4,700	618	17.5	545	5.94	8.20	1,100	4,850	639	35.0	488	11.5	51.6
113	1,247	7,000	961	15.4	626	---	12.80	1,170	5,000	640	24.6	503	---	47.8

Plasma volume decreased in all dogs in which it was measured. Extracellular fluid volume decreased in all dogs except Dog 3b in which fluid intake was not restricted and in Dog 139. Total extracellular sodium and chloride decreased in all animals except Dog 3b and total extracellular potassium, magnesium, and phosphate increased. Fluid spaces are expressed in cubic centimeters and all electrolytes are expressed in milliequivalents, including phosphate.

*Water ad libitum.

These changes have increased significance when considered in terms of alterations taking place in the extracellular fluid (Table II). There was an absolute decrease in plasma volume and extracellular fluid as measured by inulin or sucrose in almost every case, thus total extracellular sodium and chloride decreased much more than would be apparent from the plasma concentration. Total extracellular potassium, magnesium, and phosphate increased, although somewhat less than would be expected from the change in

TABLE III. CHANGES IN INTRA- AND EXTRACELLULAR FLUID AND ELECTROLYTE IN MUSCLE BIOPSIES TAKEN BEFORE AND DURING ANURIA

	EXPERIMENTAL DATA						CALCULATED DATA					
	SUCROSE OR INULIN		GROSS MUSCLE						CONCENTRATION IN CELL WATER			
DOG NUMBER	PLASMA MG./C.C.	MUSCLE MG./GM.	H_2O C.C./KG.	Na mEq./KG.	Cl mEq./KG.	K mEq./KG.	$H_2O(e)$ GM./KG.	$H_2O(e)$ GM./KG.	Na mEq./KG.	Cl mEq./KG.	K mEq./KG.	METHOD
						Controls						
3b	0.75	0.14	610	35	22	65	174	436	20	0.5	147	Inulin
117	---	---	775	42	21	93	160	615	20	---	151	Chloride
46	---	---	753	40	10	105	85	678	42	---	155	Chloride
43	---	---	749	26	11	---	91	658	20	---	---	Chloride
112	0.78	0.20	793	59	26	81	257	536	43	- 6.0	150	Inulin
139	1.35	0.46	800	69	28	84	324	476	47	-13.0	174	Sucrose
113	0.98	0.25	767	40	21	86	245	522	12	- 7.0	163	Chloride
99	0.74	0.16	762	30	18	85	222	540	20	- 9.0	156	Inulin
						Anuric						
3b	1.70	0.18	772	34	19	91	101	671	31	6.0	135	Inulin
117	3.00	0.21	745	35	29	100	66	679	37	33	147	Inulin
46	3.20	0.28	758	44	17	113	88	671	48	11	168	Inulin
43	3.73	0.27	915	46	27	120	68	847	43	22	141	Inulin
112	2.85	0.45	809	56	30	---	126	673	58	25	---	Inulin
139	1.40	0.45	826	71	43	85	302	524	57	15	159	Sucrose
113	1.55	0.46	804	47	24	94	259	545	22	0.0	144	Sucrose

Total water increased somewhat in 6 of 7 dogs. Extracellular water decreased in 5 of 7 dogs and increased only slightly in the other two. Intracellular water increased in 6 of 7 dogs. Intracellular chloride increased significantly in 3 of the 4 dogs where proper controls were available and seemed significantly increased in the 3 dogs which did not have preanuric inulin studies.

plasma concentration. An increase in the inulin space was found in Dog 3b. This was the only dog allowed an ad libitum intake of water. The intake of all the other dogs was restricted to approximately half the daily weight loss.

Table III summarizes the data derived from muscle analysis in the animals. The concentration of inulin or sucrose in the muscle biopsies of Dogs 117, 46, and 43 was too low to allow an accurate calculation of the inulin space in the specimens. The muscle concentrations in these dogs for the control period were therefore calculated on the basis of the chloride space, assuming muscle chloride to be zero. Since the inulin and sucrose studies demonstrated very little chloride outside the inulin or sucrose space in the muscle of the control animals prior to anuria (some negative values were obtained), these figures compare well with those derived from calculations based upon the inulin and sucrose spaces in the other control animals. It must be remembered that these biopsies are of fleshy muscles, low in connective tissue and cleaned of all fascia. Mokotoff and associates[12] also noted only small differences between chloride and inulin space in biopsies of human muscle.

In comparing the data from the muscle biopsies of the controls with data from the anuric animals, certain consistent changes are found. There was a decrease in extracellular fluid and an increase in intracellular fluid. No consistent change in intracellular potassium was found but intracellular sodium increased. Chloride, which was not found outside the inulin or sucrose spaces of the controls, now appeared in a greater volume of distribution than that of sucrose or inulin and thus presumably in the intracellular fluid. In general, the changes found in the muscle samples correlated with the changes in the plasma electrolytes and in the fluid spaces listed in Tables I and II.

The results of balance studies of water and chloride in 3 dogs are presented in Table IV. Chloride was lost from the extracellular space in excess of that accounted for in the excreta of the dogs over the period of anuria.

TABLE IV. CHLORIDE BALANCE IN DOGS DURING ANURIA

DOG NUMBER	CHLORIDE IN	CHLORIDE OUT	NET GAIN OR LOSS	OBSERVED LOSS IN ECF	UNACCOUNTED LOSS IN ECF
112	41.0	56.6	−15.6	−149	−165
139	97.2	118.2	−21.0	− 51	− 30
113	61.7	12.1	+49.6	−123	−173

All dogs studied lost chloride from the extracellular fluid which could not be accounted for in the fluids lost from the body and collected in the metabolic cages.

TABLE V. WATER BALANCE STUDIES ON DOGS IN ANURIA

DOG NUMBER	CONTROL WEIGHT (KG.)	WEIGHT CHANGE (KG.)	TOTAL IN (C.C.)	TOTAL OUT (C.C.)	BALANCE (C.C.)	TOTAL INSENSIBLE LOSS (C.C.)	LOSS/KILOGRAM PER DAY (C.C.)
117	15.7	−1.3	585	60	+525	1,825	38.8
46	18.6	−1.5	400	230	+170	1,670	30.0
43	18.4	−0.1	900	100	+800	900	16.0
99	21.2	−0.8	2,000	300	+700	2,500	39.3
139	17.5	−1.3	1,350	865	+485	1,785	34.0
112	16.4	−1.6	475	720	−245	1,350	27.3
113	20.9	−1.3	875	250	+625	1,925	32.0

All dogs lost weight. The daily average weight loss was 370 Gm. and the daily insensible weight loss per kilogram was 31 Gm.

Table V presents the water balance data in all dogs in which data were obtained. All fluid loss which could be measured in the metabolic cages was fully replaced but the dogs were maintained on one-half weight replacement of insensible loss to allow a daily weight loss in accord with present clinical practice. Total loss of weight averaged 7 per cent of control weight (range 1 to 10 per cent) over the 3-day period, approximately 30 mg. per kilogram per day.

Studies of total body potassium by the use of radioactive potassium are shown in Table VI. No significant change was found between the amount of available body potassium at 18 hours in the control and anuric period.

TABLE VI. RESULTS OF STUDIES OF TOTAL AVAILABLE POTASSIUM AT 18 HOURS

DOG NUMBER	SEX	CONTROL		ANURIC	
		TOTAL K	K/KG.	TOTAL K	K/KG.
117	F	374	23.8	360	25.4
46	M	915	49.2	959	56.2
3b	F	---	---	758	44.6
99	F	725	34.2	799	38.0
43	F	707	36.2	740	40.4
84	F	783	35.9	---	---
121	F	938	35.0	---	---

Total available potassium remained unchanged in the course of anuria; because of the loss of weight in the animals, the available potassium per kilogram increased somewhat.

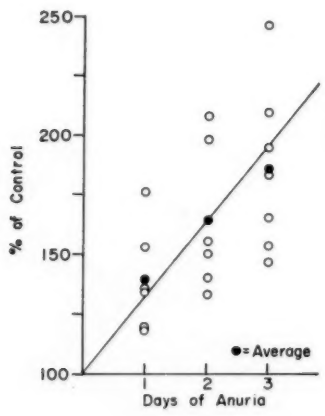

Fig. 1.

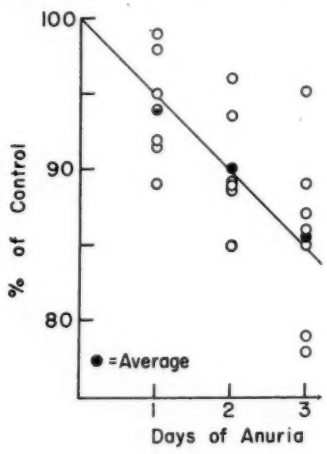

Fig. 2.

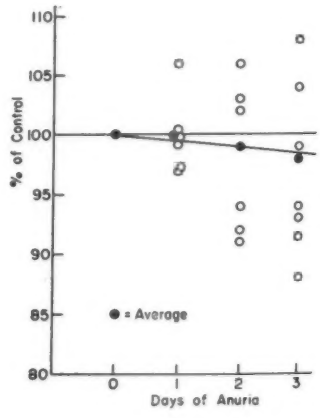

Fig. 3.

Fig. 1.—Increase in plasma potassium during anuria. The plasma potassium shows a rapid rise starting with the first day of anuria. When this change is plotted as a percentage of the plasma potassium of the control, the average daily increase appears fairly constant, giving a straight-line graph.

Fig. 2.—Decrease in plasma chloride during anuria. The plasma chloride shows a decrease starting with the first day of anuria. When this is plotted as a percentage of the plasma chloride the average daily decrease is fairly constant, giving a straight-line graph.

Fig. 3.—Change in plasma sodium during anuria. Changes in plasma sodium were quite variable and some animals showed a marked increase while others showed a decrease. The daily average of all the animals showed no significant deviation from the controls.

DISCUSSION

Figs. 1-4 illustrate the major intra- and extracellular changes in all the animals under the conditions of the experiment. There was a slight fall in plasma sodium concentration, a decrease in plasma concentration, total extracellular

chloride, total extracellular sodium, and a fall in pH. An increase in plasma and extracellular potassium, magnesium, and phosphate concentration, and total amount was seen. There was a decrease in plasma volume and in total extracellular fluid. Little change in intracellular potassium was noted. There was an increase in intracellular sodium, chloride, and water. There was a decrease in body weight.

For the sake of clarity we will discuss these variations as: (1) changes in concentration of extracellular substances, (2) changes in body weight, extracellular fluid, and plasma volume, and (3) changes in intracellular electrolytes and water.

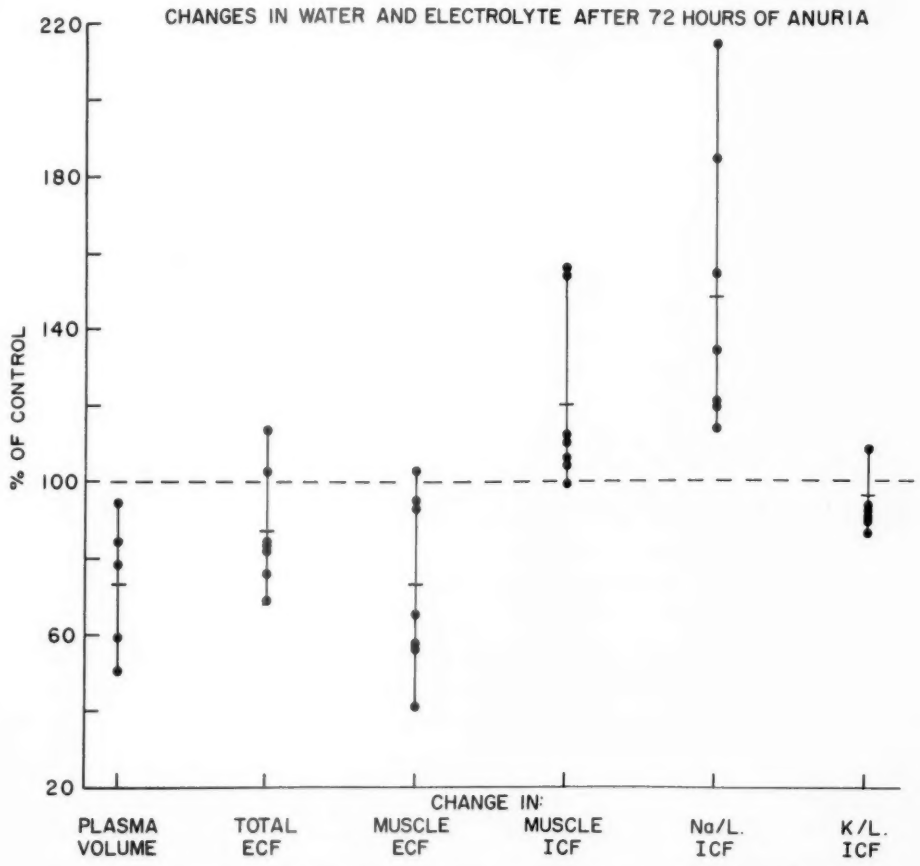

Fig. 4.—Intra- and extracellular changes of fluid and electrolyte in anuria. Plasma volume and extracellular fluid of the dog and of the muscle biopsies decreased. Intracellular water and sodium increased. The percentage of increase of intracellular chloride was off the scale of this graph. Scattergram plotted as percentage of change from the control values with the control as 100 per cent.

Changes in Concentration of Extracellular Substances.—The same changes in the plasma electrolytes, BUN, and hematocrit found in this study have been noted uniformly in renal failure, both clinical and experimental, for many years.[24, 25] The progressive straight-line change in the concentration of plasma potassium and chloride as shown in Figs. 1 and 2 is usually not so consistently seen in clinical anuria; these changes may be obscured by therapy

directed toward increasing chloride and decreasing potassium in the extracellular fluid. The magnitude of the gain or loss of these substances is better visualized when considered in terms of the total amount in the extracellular space (Table II). The rise of plasma potassium, magnesium, and phosphate is usually attributed to a release of these electrolytes from cells by catabolic processes. The decrease of sodium and especially chloride ions has been explained as due to one, two, or all of the following: loss from the body via the gastrointestinal tract, sweat, and the small amounts of urine lost in oliguria, increase in the extracellular fluid with a decrease of ion concentration by dilution, and, last, loss of ions from the extracellular space by shift into the intracellular compartment.

Changes in Body Weight, Plasma, and Extracellular Volume.—Under the conditions of these experiments, there was a considerable loss of weight in all of the dogs in which weight was determined (Table V). One would expect that this weight loss would be reflected in some degree by a decrease in plasma volume and extracellular fluid and this was the case (Table II). In addition there was a decrease in concentration of plasma sodium and chloride and thus of total extracellular sodium and chloride (Table II). This seems to rule out dilution as a cause for this change. Of the remaining routes of loss of sodium and chloride from the extracellular fluid, balance studies for chloride indicate that only moderate amounts were lost from the body and most of this was replaced (Table IV). No balance studies for sodium were carried out, but it appears unlikely that the total sodium lost from the extracellular fluid could have been lost in the small volumes of gastrointestinal tract fluids lost by some of the animals.

Changes in Intracellular Electrolytes.—If extracorporeal loss and dilution are eliminated as important factors in the change in total extracellular sodium and chloride, we are left with shift of these ions into the cells as the best explanation for the observed behavior. The muscle data (Table V) correlate well with this conclusion, demonstrating an increase in intracellular sodium and the appearance of chloride within the cells where it was previously not found in any significant amount by the techniques used. Intracellular potassium was not significantly changed, but the amount of increase found in the extracellular fluid would not be sufficient to produce an observable decrease in the intracellular concentration by the present methods. The fact that the total available body potassium did not change (Table VI) in anuria indicates that if so-called "bound stores" of potassium were present, the equilibrium with this potassium was unchanged under the conditions of the experiment.

Dog 3b must be considered separately from the others since anuria was present only 48 hours instead of 72 and the dog was allowed water ad libitum instead of being restricted. Consequently he showed an increase in extracellular volume instead of a decrease, no drop in total extracellular sodium or chloride was observed, and the drop in plasma concentration of these ions seemed to be mainly on the basis of dilution. A rise in this dog's intracellular sodium was found and intracellular chloride increased slightly. However,

no balance studies were done in this dog. Tentatively it may be said that the state of hydration plays an important role in the degree of the changes which will be found.

A number of investigators have reported an increase of extracellular fluid volume in anuria. In most of these studies the patients were overhydrated by present standards.[11, 14, 20] Moreover, some studies were based upon chloride as a measure of the extracellular fluid.[3, 11] If chloride does enter the cells in uremia, as appears to be the case,[19, 27, 28, 34] then a falsely high determination of the extracellular fluid would result from chloride space studies. Finally, in man it is almost impossible to obtain a control study prior to anuria and there is considerable variation from individual to individual of the normal extracellular fluid volume.

Recent experimental studies under rigid fluid restriction have shown a decrease in the plasma volume or extracellular fluid in rabbits, sheep, dogs, and man.[9, 10, 13, 14] Hamburger and Mathe[9] produced renal failure in dogs by ligation of the ureters and found a decrease in the thiocyanate space in these animals over a period of 3 to 4 days. These studies closely duplicate the first portion of our work and were unknown to us when our experiments were done. The investigators also discovered that the effective osmotic pressure in anuria (as contrasted to the total osmotic pressure) is reduced and suggest a shift of water from the extracellular fluid into the cells. The consistent increase of intracellular water found in our muscle biopsies is in substantial agreement with this.

The observation that there is a rise in the intracellular levels of sodium and chloride and a rise in the extracellular levels of the important intracellular ions of potassium, magnesium, and phosphate leads to the suggestion that the normal mechanisms of the cell membrane which operate to partition these ions have been impaired. Somewhat similar changes have been found in tissues injured by anoxia, direct trauma, and burns.[6, 7, 15, 17]

Although the total milliequivalents of sodium lost from the extracellular compartment are greater than the total milliequivalents of chloride lost, the plasma concentration of sodium is better maintained than is the chloride concentration (Figs. 2 and 3). This may be due to the existence of reservoirs of sodium in bone acting to stabilize the plasma concentration.[1]

A word must be said concerning the role of inulin as used in this study. Some investigators have felt that inulin penetrates the intracellular space during uremia.[5] Such a shift, if it is of any magnitude, would erroneously indicate an increase in the inulin space of the animals and of the muscle biopsies, that is, intracellular fluid would appear to decrease and extracellular fluid to increase, exactly the opposite of the changes found. Swann and associates[23] have demonstrated a consistent extrarenal clearance of inulin, sucrose, mannitol, thiocyanate, and radiosulfate in anuria, but the hourly loss of these substances is small in most instances and can be compensated as was done here by allowing the same period of time for equilibration in the control and anuric animals. Sucrose was used in 2 animals because it may, as Swann and his

group pointed out, represent more nearly the true extracellular fluid than does inulin. However, in computing the changes from the control to the anuric state when each animal is used as its own control, the absolute values of the fluid compartments cancel out and the degree and direction of change remain the same.

SUMMARY AND CONCLUSIONS

1. Anuria was created in mongrel dogs by ligature of the ureters. Studies of intra- and extracellular fluid spaces and electrolytes were done before and usually 72 hours after the onset of anuria. In all but one dog fluid intake was restricted to approximately one-half of the insensible loss.

2. During anuria total extracellular sodium, chloride, carbon dioxide, and pH decreased; extracellular potassium, phosphate, and magnesium increased. Intracellular sodium and chloride increased.

3. With fluid restriction plasma volume decreased; inulin or sucrose space decreased both in the entire animal and in muscle biopsies; and intracellular water increased.

4. Balance studies indicated that the loss of chloride from the extracellular fluid could not be accounted for in extracorporeal losses.

5. Total available body potassium remained the same before and during anuria.

6. It was felt that under the conditions of these experiments there is a shift of fluid and electrolytes from the extracellular space into the cells with extracellular dehydration, hyponatremia, and hypochloremia correlated with intracellular edema, hypernatremia, and hyperchloremia.

7. Possible explanations for these changes are discussed.

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SURVIVAL OF THE EXCISED DOG KIDNEY PERFUSED IN A PUMP-OXYGENATOR SYSTEM

I. Circulatory Changes in the Hypothermic Preparation

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INTRODUCTION

THE limitations of the excised kidney perfusion preparation as a method for physiologic study include brevity of "steady-state" periods, low glomerular filtration rate, abnormal tubular function, and limited duration of survival. Despite these difficulties, Starling and Verney,[26] Winton,[27] and others have conducted informative studies of renal hemodynamics, oxygen metabolism, and urine excretion.

The advent of renal isotransplantation in the human being as curative therapy for renal failure[17, 19] and recent insights into the immune mechanisms of tissue homograft rejection have suggested the application of artificial perfusion techniques to studies of the homograft rejection response, of donor antigen transformation, and of whole-organ storage. To be useful in the first two instances, the device should enable survival for many hours or preferably for days. For tissue storage, it should support viability for at least 3 hours, that is, the approximate upper limit of time that human[14] and canine[10, 18] kidneys will survive in total ischemia.

If capacity to sustain life after perfusion and replantation is the criterion of kidney viability, investigations to date are disappointing.[5] Moreover, excised dog kidneys will not survive immersion in cooled static media for more than 4 hours.[23]

Although the question of impaired viability—as distinct from impaired function—is obviously central to all physiologic studies employing excised kidney perfusion, published data on this subject are rather sparse. Bainbridge and Evans[1] demonstrated in 1914 that inclusion of an animal lung in the blood circuit would increase renal blood flow and improve function, but the duration of survival in such preparations is still limited to about 6 hours. Kupfer, Thompson, and Pitts[16] made a detailed study of the pump-lung preparation with regard to impairment of glomerular filtration rate, p-aminohippuric acid

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clearance, creatinine urine/plasma ratio, and rate of sodium excretion; the duration of their preparations was also about 6 hours. Bayliss and Ogden[2] outlined their experience with a system in which an animal lung was *not* included. Using rubber tubing, they found that blood flow could be increased by using very small quantities of blood (70 ml.), and that the upper limit of such flow was 50 to 75 per cent of normal. The duration of survival was not stated.

Bickford and Winton,[3] in studying canine pump-lung kidneys, remarked briefly that duration of survival under hypothermia was prolonged. At 25° C., there was a 25 per cent reduction of blood flow, as compared with the flow at 38° C.; the urine flow was nearly doubled, the creatinine urine/plasma ratio was decreased by about 50 per cent, and there was usually about a 20 per cent reduction of creatinine clearance (the latter, at 38° C., was 6 to 7 ml. per minute). Below 18° C., the kidneys performed minimal osmotic work, and the urine approximated a plasma ultrafiltrate.

The present studies comprised the first phase of our efforts to sustain viability in excised kidneys for extended time periods, without passage of the perfusing blood through lung tissue. It seemed logical to begin with experiments utilizing the known advantages of hypothermia, highly heparinized blood, and a reasonably simple apparatus containing siliconized glass, Tygon tubing, and a minimally traumatic pump.

These studies were planned (a) to determine the survival time of such preparations and (b) to document some of the hemodynamic and functional factors associated with failure. The studies are divided, in the subsequent discussion, into the following 3 phases: (1) performance of the excised dog kidney when perfused with whole autologous blood at 25° C., without addition of solutes or diluents during perfusion (Group A, 5 preparations), (2) effects of elevated and normal plasma sodium concentrations on renal blood flow, with concomitant depression of hematocrit and solutes other than those added (arbitrarily called ulterior solutes* hereinafter) (Groups B and C, 9 preparations), and (3) response of creatinine clearance, creatinine filtration fraction, and tubular reabsorption of water as related to plasma dilution with isonatronic sodium chloride (Groups D_1 and D_2, 6 preparations).

METHODS

Operative Procedure.—In all experiments, mongrel dogs (weight range 14 to 20 Kg.), randomly selected and in apparent good health, were used. Anesthesia was by intravenous sodium pentobarbital (30 mg. per kilogram).

Through a midline incision, the kidney and its vessels were dissected. The artery, vein, and ureter were clamped at a suitable distance from the kidney and divided. Cannulation with polyethylene tubing was followed by gentle flushing of the organ with 10 ml. of isotonic saline and 10 mg. of sodium heparin.

Blood was obtained by femoral cannulation and collection in polyvinyl (Fenwal) bags containing 80 mg. (8,000 units U.S.P.) sodium heparin per

*The term *ulterior solutes* refers to all solutes normally present in the perfusate *other than* those present in the added diluent solutions.

600 ml. capacity. The perfusion apparatus was filled with blood, the kidney was inserted, and perfusion was begun. The average ischemic interval was about 30 minutes.

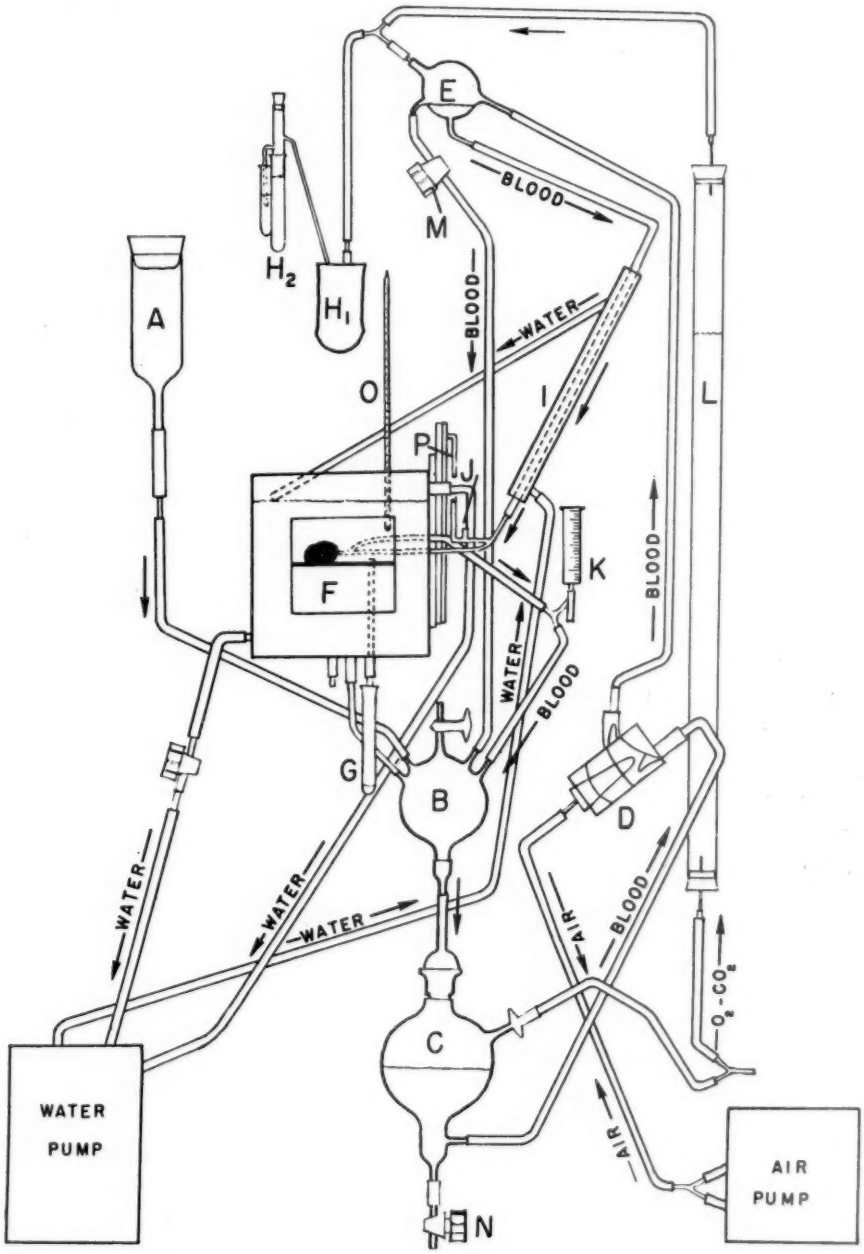

Fig. 1.—Diagram of perfusion system.[12] Apparatus is filled through vessel *A*, whence the perfusate is conducted to junctional sphere *B* and reservoir *C*. Ventricle *D*, equipped with siliconized rubber flutter valves, contains a pulsatile finger cot which impels perfusate upward to pressure-oxygenation sphere *E*. Gas mixture (95 per cent O_2, 5 per cent CO_2) is hydrated in cylinder *L* and conducted to *E* where film oxygenation takes place. Pressure is maintained at 100 mm. Hg by mercury valve H_2, when valve *M* is closed. From *E* blood passes through water jacket *I* to the kidney in chamber *F*. Arterial samples are removed at *J*, and arterial pressure is measured at manometer *P*. The venous outflow returns to junctional vessel *B*. Flow measurements are made at syringe *K*. Urine is collected in tube *G*. Temperature of water in jacket *I* and perfusion box is maintained by thermostat and coil in water pump.

Perfusion Apparatus and Procedure.—The apparatus, depicted in Fig. 1, was a modification of the system used at the Worcester Foundation for Experimental Biology.*[12] It consisted of Tygon tubing, siliconized glass vessels, and a "ventricular," pulsatile-cot pump in series with the kidney. No excised dog lung was used. Oxygen (95 per cent) and carbon dioxide (5 per cent) were passed through a 3 foot water column, at a rate of about 1 L. per minute, into the uppermost glass sphere, where blood oxygenation and gas pressure were maintained. The arterial pressure was kept constant at the desired level (130 to 140 mm. Hg) by action of the mercury valve. The kidney chamber temperature was maintained at 25.5° ± 0.5° C., as was the perfusing blood in the adjacent arterial segment.

The wet weight of the kidney was obtained before and after perfusion. Blood flow measurements were made by frequent timed collections of venous blood in a calibrated syringe. Arterial and venous blood specimens were removed at appropriate intervals to coincide with removal of urine specimens. Urine volumes were read at 5- to 10-minute intervals, depending upon magnitude of flow, and specimens were taken for analysis after suitable washout periods.

Chemical Analyses.—The blood specimens were immediately centrifuged and hematocrit values were determined. The plasma was analyzed, depending upon the experimental group, for sodium, potassium, total solutes, and creatinine. The sodium and potassium levels were determined on a Baird Associates internal standard flame spectrophotometer. Total solutes were determined by freezing-point depression in a Fiske osmometer. The creatinine concentration was measured by the Jaffe reaction.[11]

EXPERIMENTAL GROUPS

Control Preparations (Group A, 5 Preparations).—

Perfusion was carried out as described without addition of solutes or diluents. The course of blood and urine flow was traced until the blood flow reached 0.25 ml. per gram of kidney per minute.

Results: The data are recorded in Table I, and graphic representation of the renal blood flow values, with intervals of urine production, appears in Fig. 2. The performance of these kidneys passed through 3 phases. Phase I, when blood flow declined precipitously to approximately 50 per cent of the starting level, was complete for all preparations within the first 10 minutes.† The second phase, the period of urine flow, was the interval from the end of phase I to the point where urine flow fell to less than 0.1 ml. per minute. The renal blood flow during this phase declined very gradually over a period of widely varying length (55 to 160 minutes). As would be predicted, the variation of urine flow

*We owe much to the generosity of Dr. Oscar Hechter and Mr. Austin Fish for their loan of equipment in the initial stages of the work.

†When expressed as the absolute value, the decline of blood flow does not yield a significant p value by the Gosset-Fisher t test, due to the large standard deviation created by the excessive decrease in K.P. 40-1. When expressed as *per cent of initial value*, however, t becomes 4.47 and p less than 0.02. The equation used: t = mean of the change in flow sample standard.

TABLE I. COURSE OF BLOOD AND URINE FLOW IN AUTOLOGOUS BLOOD PERFUSED DOG KIDNEYS
(GROUP A CONTROLS)

EXPERIMENT NUMBER	WEIGHT OF KIDNEY (GM.)	INITIAL RENAL BLOOD FLOW (ML./GM./MIN.)	RENAL BLOOD FLOW FALL FIRST 10 MIN.		DURATION OF PHASE I (MIN.)	PHASE II			PHASE III		DURATION RENAL BLOOD FLOW (MIN.)	WEIGHT GAIN (PER CENT)
			ABSOLUTE	PER CENT		RENAL BLOOD FLOW (MID-PHASE)	PEAK URINE FLOW (ML./MIN.)	DURATION (MIN.)	RENAL BLOOD FLOW (MID-PHASE)	DURATION (MIN.)		
46	46.4	1.12	0.26	23.2	5	0.50	0.70	160	0.30	75	240	29.1
47	46.4	0.86	0.56	66.0	5	–	–	–	0.40	25	29	7.6
48	51.4	1.72	0.48	27.9	10	1.10	2.85	60	0.30	5	75	29.6
49	37.5	1.39	0.83	59.5	10	0.70	0.30	55	0.40	300(+)	360(+)	34.4
40-1	40.0	2.30	1.95	84.5	5	0.30	0.10	70	–	–	75	31.0
Mean		1.45	0.82	52.2	6.8	0.65	1.0	86	0.35	100(+)	157	26.3
Range		0.86-2.30	0.26-1.95	23.2-84.5	5-10	0.30-1.10	0.10-2.85	55-160	0.30-0.40	5-300(+)	29-360(+)	7.6-34.4
Standard deviation			±0.70	±26.1								
t			2.69	4.47								
p			>0.1	<0.02								

The data outline the course of hemodynamic and excretory failure in excised, whole-blood perfused kidneys in the absence of perfusate dilution. Note the precipitous fall of renal blood flow in the first 10 minutes of perfusion. The data are depicted graphically in Fig. 2.

in this randomly selected group of dogs was also wide. In Experiment 47, urine flow was barely detectable, thus making impossible a delimitation of phase II.

Phase III, the terminal period, was the interval from the endpoint of urine flow (0.1 ml. per minute) to the endpoint of blood flow (0.25 ml. per gram of kidney per minute). In Experiments 40-1, phase III was technically absent, since the renal blood flow reached its terminal point coincident with the endpoint of urine flow.* The midpoint blood flow of phase III was 0.35 ml. per gram of kidney per minute with a range of 0.3 to 0.4. In only one of the 5 experiments did urine formation occur below this level of blood flow.

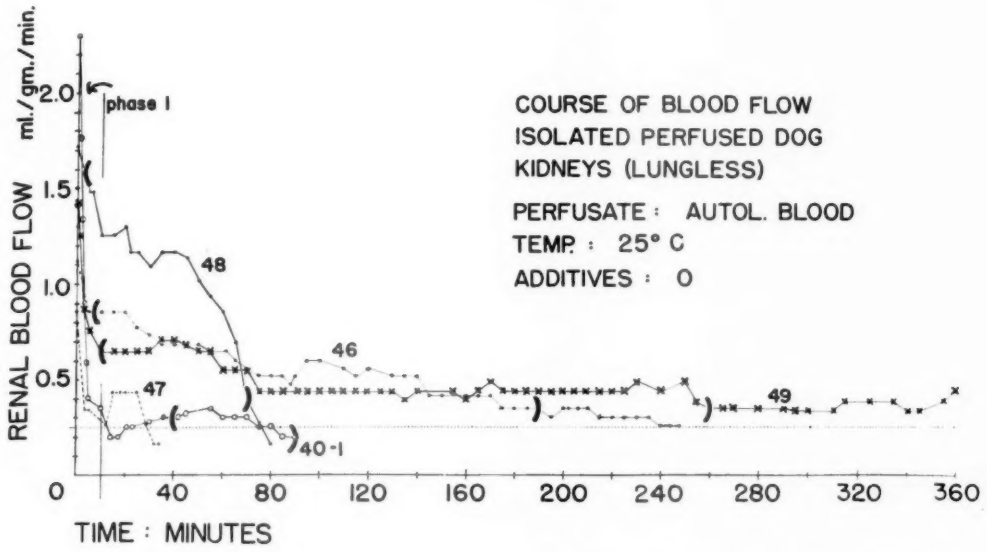

Fig. 2.—The natural history of blood and urine flow in control perfused kidneys (data from Table I). The brackets indicate the intervals over which urine was excreted; the numbers are those of the experiments. Note that blood flow in all kidneys is at the 0.5 ml./gram/minute by 80 minutes. RBF = renal blood flow; RPF = renal plasma flow; U/P = urine/plasma.

Weight gain in the 4 experiments surviving 60 minutes or longer ranged from 29.1 to 34.4 per cent of initial weight; the single kidney with a short survival period gained 7.6 per cent.

The extremely wide variation of circulatory survival time, that is, the sum of all 3 phases of performance, contrasted with the lesser variation and usually much shorter duration of excretory survival time, that is, the sum of phases I and II.

Effects on Renal Blood Flow and Urine Flow of Perfusate Dilution by Hypernatronic and Isonatronic Sodium Chloride Solutions and by 5 Per Cent Glucose in Water.—

Hypernatronic Sodium Chloride Addition (Group B, 5 Preparations).— After a control period of about one hour, sodium chloride solution (1,200 mEq. NaCl per liter) was added to raise the plasma sodium concentration to the range

*The urine and blood flow endpoints were arbitrarily selected after preliminary experience indicated that urine formation ceased, in the majority of experiments, beyond these points. Our criteria of viability are not yet adequate to identify the true point of irreversible injury.

of 250 to 300 mEq. per liter. After the urine flow subsided to approximately the base line level, sufficient 5 per cent glucose in water was added to reduce the plasma sodium concentration to normal.

TABLE II. COURSE OF BLOOD AND

GROUP B		CONTROL PERIOD				HYPERNATRONIC DIURESIS						
EXPERIMENT NUMBER	KIDNEY WEIGHT (GM.)	PLASMA (MEQ./L.) NA	K	NA/K	HEMATOCRIT	PLASMA (MEQ./L.) NA	K	NA/K	HEMATOCRIT	RENAL BLOOD FLOW RISE (ML./GM./MIN.) ABSOLUTE	(PER CENT)	URINE FLOW RISE (PER CENT)
27	43.4	155	3.2	48.5	0.43	270	1.5	180	0.31	1.48	400	490
28	39.5	150	3.0	50.0	0.41	320	2.0	160	0.33	0.82	83.0	2,400
29	36.0	165	2.6	63.5	0.35	290	1.1	264	0.31	0.33	42.5	700
30	34.0	158	2.3	68.8	0.43	245	1.5	163	0.34	0.44	33.0	285
31	33.0	150	3.7	40.6	0.41	250	1.8	139	0.37	0.49	66.0	625
Mean	37.2	156	2.8	54.3	0.40	275	1.6	181	0.33	0.71	124.9	900
Range	33.0-43.4	150-165	2.3-3.7	40.6-68.8	0.35-0.43	245-320	1.1-2.0	139-264	0.31-0.37	0.33-1.48	33-400	285-2,400
Standard deviation										±0.35	±155	
t										4.48	1.8	
p										<0.02	>0.1	

GROUP C		CONTROL PERIOD				ISONATRONIC DIURESIS						
EXPERIMENT NUMBER	KIDNEY WEIGHT (GM.)	PLASMA (MEQ./L.) NA	K	NA/K	HEMATOCRIT	PLASMA (MEQ./L.) NA	K	NA/K	HEMATOCRIT	RENAL BLOOD FLOW RISE (ML./GM./MIN.) ABSOLUTE	(PER CENT)	URINE FLOW RISE (PER CENT)
33	52.5	160	3.0	53.5	0.54	160	1.5	107	0.37	1.08	108	685
34	43.0	165	3.0	55.0	0.49	165	1.2	137	0.33	0.38	51.5	218
37	42.0	145	3.9	37.2	0.43	149	1.7	88	0.38	0.40	100.0	360
30-1	42.6	153	3.0	51.0	0.51	152	1.2	127	0.46	0.85	152.0	390
Mean	45.0	156	3.2	49.1	0.49	156	1.4	115	0.38	0.67	102.9	413
Range	42.0-52.5	145-165	3.0-3.9	37.2-55.0	0.43-0.54	149-165	1.2-1.7	88-137	0.33-0.46	0.38-1.08	51.5-152.0	218-685
Standard deviation										0.35	0.41	
t										3.82	5.02	
p										<0.05	<0.02	

Group B.—Primary data describing the course of blood and urine flow in kidneys subjected to hypernatronic saline dilution of perfusate, followed by dilution wth 5 per cent glucose in water. Note the range over which the decreases of hematocrit occurred and the corresponding rise of blood flow. In all instances, the diuresis was so great that hematocrit rose above its prediuretic level.

Isonatronic Sodium Chloride Addition (Group C, 4 Preparations).—After a 1-hour control period, sufficient isonatronic sodium chloride (146 mEq. per liter) was added to the perfusate to reduce the hematocrit to the range of 35 to 45 and the ulterior solutes by about 50 per cent. After subsidence of the diuresis, a quantity of 5 per cent glucose in water was added to reduce the plasma sodium concentration to the range of 125 to 135 mEq. per liter.

Results: The data from these 2 groups of experiments are recorded in Table II. Fig. 3 depicts the course of a representative preparation from Group C; the course of blood and urine flow in the hypernatronic sodium chloride experiments (Group B) was similar.

In Group B, addition of hypernatronic sodium chloride was followed by a significant increase of renal blood flow.* The hematocrit values after completion of diuresis exceeded the predilution values in all cases. In 3 of the 5 cases,

URINE FLOW IN PERFUSED KIDNEYS

PERIOD		5 PER CENT GLUCOSE IN WATER DIURESIS PERIOD										
						RENAL BLOOD FLOW RISE (ML./GM./MIN.)						
DURATION DIURESIS (MIN.)	HEMATOCRIT POST-DIURESIS	PLASMA (MEQ./L.) NA	K	NA/K	HEMATOCRIT	ABSOLUTE	(PER CENT)	URINE FLOW RISE (PER CENT)	DURATION DIURESIS (MIN.)	HEMATOCRIT POST-DIURESIS	DURATION SURVIVAL (MIN.)	WEIGHT GAIN (PER CENT)
90	0.50	165	1.00	165	0.45	0	0	203	70	0.55	255	58.0
65	0.50	144	0.70	206	0.31	1.01	100.0	343	100	0.56	255	67.0
100	0.44	151	0.74	204	0.38	0	0	0	0	0.36	245	47.2
70	0.61	166	0.68	244	0.44	0.35	42.0	194	80	0.63	210	53.0
120	0.48	160	0.80	200	0.42	0.12	8.2	300	180	0.51	340	54.5
89	0.53	157	0.78	203	0.40	0.28	30.0	208	86	0.52	261	55.9
65-120	0.44-0.61	144-166	0.7-1.0	165-244	0.31-0.45	0-1.48	0-100	0-343	0-180	0.51-0.63	210-340	47.2-67

PERIOD		5 PER CENT GLUCOSE IN WATER DIURESIS PERIOD										
						RENAL BLOOD FLOW RISE (ML./GM./MIN.)						
DURATION DIURESIS (MIN.)	HEMATOCRIT POST-DIURESIS	PLASMA (MEQ./L.) NA	K	NA/K	HEMATOCRIT	ABSOLUTE	(PER CENT)	URINE FLOW RISE (PER CENT)	DURATION DIURESIS (MIN.)	HEMATOCRIT POST-DIURESIS	DURATION SURVIVAL (MIN.)	WEIGHT GAIN (PER CENT)
80	0.45	135	1.0	135	0.39	0	0	171	60	0.43	290	36.0
120	0.35	130	0.7	186	0.32	0.09	10.7	200	50	0.36	215	53.5
75	0.46	124	1.5	83	0.40	0	0	147	110	0.46	235	38.8
155	0.52	134	0.8	167	0.50	0	0	161	85	0.57	315	41.0
107	0.44	131	1.0	143	0.40	0.02	2.5	170	76	0.45	264	42.4
75-155	0.35-0.52	124-135	0.7-1.5	83-186	0.32-0.50	0-0.09	0-10.5	147-200	50-110	0.36-0.57	215-315	36-53.5

Group C.—Primary data describing the course of blood and urine flow in kidneys subjected to isonatronic saline dilution of perfusate, followed by dilution with 5 per cent glucose in water. The glucose additions in this group were smaller than those in Group B since it was desired to reduce the plasma sodium concentration no lower than 125 mEq./L. Note the corresponding lack of blood flow increase in the second diuretic phase.

an increase of blood flow also followed addition of glucose, although this was always given in the latter portion of the procedure when the blood flow was declining. The addition of glucose solution was accompanied by return of plasma sodium concentration to nearly the control levels, while the further decrease of potassium concentration served, as in the Group C experiments, as a rough index of the decrease in concentration of the other ulterior solutes. The hematocrit in all experiments was 31 or greater.

*Due to the widening of the standard deviation by the extreme percentagewise increase of Experiment 27, the t test gives a p value greater than 0.1. However, if the last 4 experiments are considered alone, p is less than 0.05. Moreover, if all 5 responses are tested by their absolute values of blood flow increase, p is less than 0.02.

In Group C, where *no* significant change of plasma sodium concentrations was produced in the first diuretic phase, the addition of isonatronic sodium chloride was nevertheless followed by a significant increase of blood flow. No important difference in blood flow response was noted between Groups B and C with reference to high and normal plasma sodium levels.*

In the Group C preparations, the hematocrit values remained well above 30 in all cases. Three of the 4 kidneys failed to respond to the 5 per cent glucose solution with a rise of blood flow; the corresponding reductions of hematocrit were less than in the glucose phase of Group B.

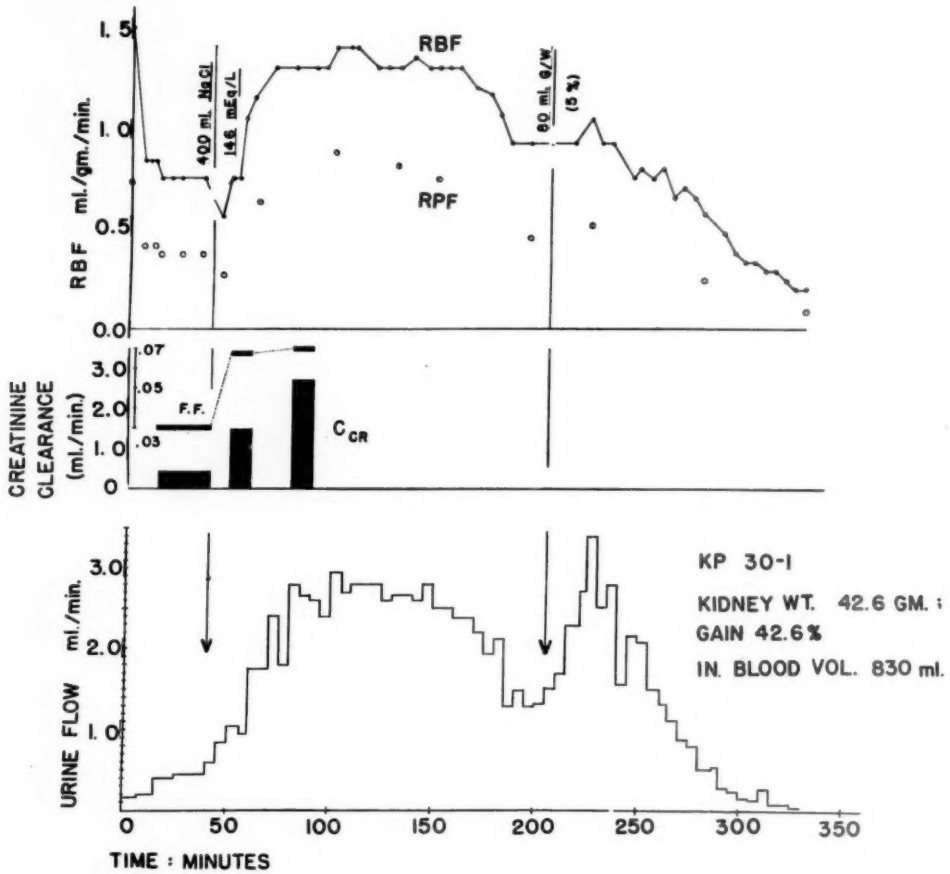

Fig. 3.—Course of a typical experiment, when treated with saline dilution, illustrating rise of renal plasma flow (RPF), urine flow, creatinine clearance (CCr), and filtration fraction (FF) (clearances by endogenous creatinine). RBF = renal blood flow.

The mean relative weight gain in the kidneys treated with hypernatronic saline was about 56 per cent, with a range of 47 to 67 per cent; the mean relative weight gain in the kidneys treated with isonatronic saline was about 42 per cent, with a range of 36 to 53 per cent. Similarly, there was no significant difference between the durations of survival of the 2 groups. Chiefly because

*For the absolute change of blood flow, p was less than 0.05; for the per cent change of flow, p was less than 0.02. The increase of flow in Group C was nearly equal to the increase in Group B.

of the large variance in the control group (A), no significant increase of circulatory survival time can be demonstrated in this small number of experiments, although it is strongly hinted.

Patterns of Creatinine Clearance, Filtration Fraction, and Creatinine Urine/Plasma Ratio Following Dilution With Isonatronic Sodium Chloride (Groups D_1 and D_2, 6 Preparations).—

In these groups, changes of creatinine clearance and filtration fraction were observed in correlation with saline-induced changes of plasma flow. The creatinine urine/plasma ratio was used as a simple index of tubular water reabsorptive capacity.

In Group D_1, in order to obtain creatinine clearance values without addition of exogenous solutes, endogenous creatinine concentrations were estimated from total creatinine-like chromogens. Because the proportion of noncreatinine, alkaline-picrate-reacting chromogens in the plasma can be expected to increase with time (due to their low clearance[25]) and thereby increase error, samples for this analysis were not taken at later than 100 minutes of perfusion.* Two of these preparations appear in Group C; the third was performed in the same manner.

In Group D_2, 4 perfusions were performed wherein a quantity of creatinine-Locke's solution (250 mg. creatinine per 100 ml. Locke's solution) was given initially and after subsidence of the last saline diuresis; the infusion rate was at one-tenth the estimated plasma flow. Because of variation of the latter and variation of creatinine clearance, the plasma creatinine levels among kidneys varied from 7.5 to 17.5 mg. per 100 ml. For a given preparation, however, the level was reasonably uniform. The isonatronic saline, containing 25 mg. creatinine per 100 ml., was added twice in each perfusion experiment. The preparations were followed for the duration of survival.

The ratio X_2/X_1 was used to indicate the maximum reduction of the ulterior solute concentrations occurring after dilution.†

Results: The observed data are recorded in Table III, *A*; in Table III, *B* are recorded the computed data for creatinine urine/plasma ratio, clearance, and filtration fraction. The mean value of X_2/X_1 was 0.59 with a range of 0.44 to 0.72, thus indicating an average decrease of ulterior solutes concentration of about 40 per cent.

All experiments of Group D showed significant increases of creatinine clearance and filtration fraction after saline.‡ The percentage increase of creatinine clearance varied from 50 to 500 per cent, and the percentage increase of filtration fraction ranged from 53 to 465 per cent.

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*Since the error favors an erroneously high estimate of plasma creatinine chromogen, the values derived from the clearance expression (U.V/P) would be underestimated. Any positive change, however, must be real since this type of error would cause bias *against* such change—particularly if considerable urine output occurred between the control period and test period samplings.

†Where X_2 = solute concentration after dilution, X_1 = solute concentration before dilution, and Hct_2 and Hct_1 the corresponding hematocrit values, $\frac{X_2}{X_1} = \frac{Hct_2\ (1\text{-}Hct_1)}{Hct_1\ (1\text{-}Hct_2)}$.

‡For Groups D_1 and D_2 considered together, the mean rise of creatinine clearance was 2.53 ml. per minute, and p less than 0.05; the mean rise of filtration fraction was 0.058, with p less than 0.005.

TABLE III

EXPERIMENT NUMBER	A. RESPONSE OF CREATININE CLEARANCE AND FILTRATION FRACTION TO ISONATRONIC SODIUM CHLORIDE										
	AT LOW POINT OF CREATININE CLEARANCE PRECEDING RISE						POSTSALINE AT PEAK OF CREATININE CLEARANCE				
	WEIGHT (GM.)	HEMATOCRIT	RENAL BLOOD FLOW (ML./GM./MIN.)	URINE FLOW (ML./MIN.)	CREATININE CONCENTRATION		HEMATOCRIT	RENAL BLOOD FLOW (ML./GM./MIN.)	URINE FLOW (ML./MIN.)	CREATININE CONCENTRATION	
					URINE	PLASMA				URINE	PLASMA
Group D_1											
34	43.0	0.34	0.93	1.5	3.0	2.25	0.32	0.93	3.2	0.94	1.0
30-1	42.6	0.52	0.56	0.45	7.9	8.0	0.37	1.32	2.7	2.6	2.6
38	53.4	0.48	0.91	0.60	6.4	6.4	0.38	1.29	1.6	3.75	2.6
Group D_2											
30-3	39.5	0.40	0.81	0.30	24.0	16.2	0.38	0.71	1.05	36.0	17.5
30-4	55.1	0.47	0.45	0.37	37.5	17.5	0.43	0.98	2.7	27.5	17.5
30-6	57.5	0.52	1.39	0.96	52.5	7.5	0.42	1.74	5.8	22.5	11.3

EXPERIMENT NUMBER	B. DATA COMPUTED FROM PRIMARY DATA OF A												
	AT LOW POINT OF CREATININE CLEARANCE			POSTISONATRONIC SALINE AT PEAK OF CREATININE CLEARANCE AND FILTRATION FRACTION									
	CREATININE URINE/PLASMA RATIO	CREATININE CLEARANCE	FILTRATION FRACTION	MAXIMUM X_2/X_1 RATIO	RENAL PLASMA FLOW CHANGE (ML./GM./MIN.)		CREATININE URINE/PLASMA RATIO	CREATININE CLEARANCE (ML./MIN.)	CREATININE CLEARANCE RISE (ML./MIN.)		PEAK FILTRATION FRACTION	FILTRATION FRACTION RISE	
					ABSOLUTE	PER CENT			ABSOLUTE	PER CENT		ABSOLUTE	PER CENT
34	1.33	2.0	0.075	0.49	+0.02	+3.2	0.94	3.00	1.0	50	0.115	0.040	53
30-1	1.00	0.45	0.031	0.54	+0.56	+208	1.0	2.70	2.25	500	0.077	0.042	135
38	1.00	0.60	0.021	0.61	+0.33	+70	1.45	2.30	1.70	284	0.056	0.035	167
30-3	1.48	0.45	0.022	0.44	−0.05	−10.2	2.05	2.15	1.70	368	0.124	0.102	465
30-4	2.14	0.79	0.060	0.72	+0.32	+133	1.57	4.25	3.45	440	0.137	0.077	128
30-6	7.00	6.7	0.178	0.64	+0.32	+48	2.0	11.6	7.75	200	0.233*	0.055	106
Mean		1.9	0.062					4.33	2.53		0.124	0.058	
Range		0.45-6.7	0.021-0.178					2.15-11.6	1.0-7.75		0.056-0.233	0.035-0.102	
Standard deviation									±2.54			±0.026	
t									2.45			5.46	
p									<0.05			<0.005	

Primary and computed data demonstrating the increase of creatinine clearance and filtration fraction following isonatronic saline. The low points of initial decline of creatinine clearance in Experiments 34, 30-3, and 30-4 were not reached until shortly after the isonatronic saline was given; this low point was then followed by a rise to the peak levels recorded. The ratio X_2/X_1 indicates the degree of reduction of solutes other than sodium and chloride between the beginning of perfusion and the period of minimum hematocrit.

*Peak filtration fraction in this experiment did not coincide with the peak creatinine clearance; it is calculated from a creatinine clearance of 8.75 ml. per minute and renal plasma flow of 37.6 ml.

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In Fig. 3, this effect is demonstrated in an experiment from Group D_1 and, in Fig. 4, in an experiment of somewhat longer duration from Group D_2. In the former preparation, the creatinine clearance increased in linear relation with

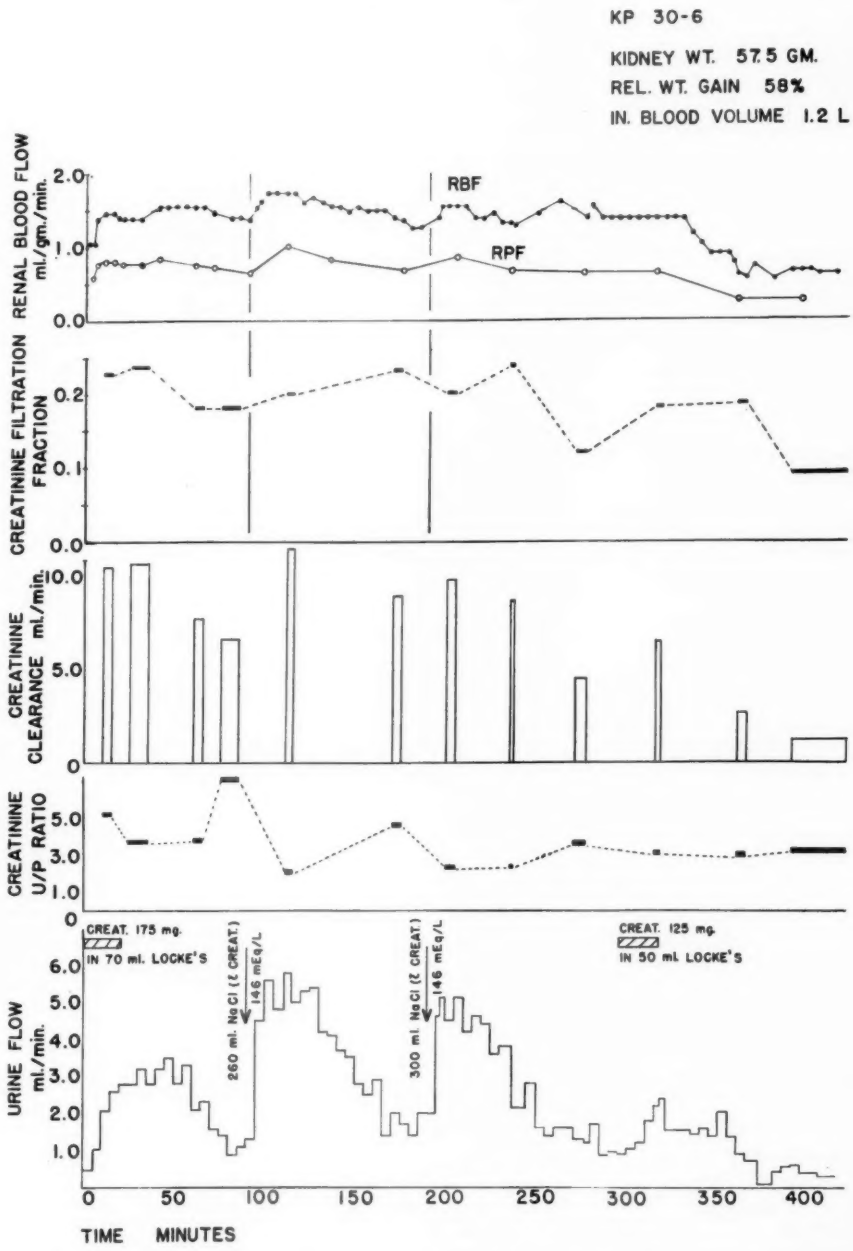

Fig. 4.—Course of renal plasma flow, urine flow, urine plasma ratio, exogenous creatinine clearance, and filtration fraction in a 420-minute perfusion experiment (from Group D_2).

the urine flow, since the urine/plasma ratio remained approximately at unity (Table III *A*). Since the creatinine clearance rose proportionately more than the renal plasma flow, the filtration fraction also increased.

In the experiment depicted in Fig. 4, the control period showed a decline of creatinine clearance, which was reversed within 25 minutes after the isonatronic saline was added. The filtration fraction did not reach its peak (0.23) until the renal plasma flow and urine flow were declining after the second administration of isonatronic saline, but the highest recorded creatinine clearance value (11.6 ml. per minute) came near the peak of the first diuresis. During the terminal decline of renal blood flow (330 to 420 minutes) from 1.39 to 0.35 ml. per gram of kidney per minute—a decline of 75 per cent—the filtration fraction declined by 50 per cent.

In all 3 of the kidneys of Group D_2, there was an increase of renal blood flow during the first 10 minutes, in place of the severe fall, in association with the initial loading dose of creatinine-Locke's solution.

The duration of survival in the 3 kidneys of D_2 was 7 hours.

DISCUSSION

Passage of the perfusing blood through lung tissue, although enabling higher renal blood flow, does not assure prolonged survival, adds to the technical complexity of the procedure, and introduces a poorly understood variable.* Moreover, subnormal blood flow may not necessarily indicate inadequate viability for storage purposes, especially under hypothermia. The use of an animal lung was therefore omitted.

Homologous blood, although technically advantageous, was avoided in order to exclude the possibility of transfusion reactions. Although dogs carry differing blood group antigens,[28] renal failure attributable to blood group incompatibility is rarely, if ever, a problem in the dog.

Performance of the Excised Kidney Perfused With Whole Blood Alone.—The precipitous decline of blood flow during the first 10 minutes in the Group A kidneys indicates that the factors responsible were present in the system initially and were rapidly acting. Total vascular occlusion did not occur, however. The pattern of a fast decrease of flow (phase I), followed by a slower period of decline (phases II and III), suggests the presence of 2 or possibly more agencies. Bayliss and Ogden,[2] reasoning on different grounds, hypothecated that there were both "temporary" and "permanent" vasoconstrictors.

Richards and Plant[22] found that as little as 0.2 mcg. of adrenalin per kidney would produce vasoconstriction in rabbit and dog kidneys. Bollman, Maher, and Manger[4] found that loss of one-third of the blood volume in normal dogs would cause the total catechol amine levels to rise from a control value of about 3.5 to 11.5 mcg. per liter—approximately 55 times the Richards-Plant dose. Further bleeding caused still greater increases of catechol amine concentration. Studies are in progress to determine free plasma catechol amine levels of the blood used in the perfusion experiments described.

Angiotonin and renin have marked vasoconstrictor effects which have already been demonstrated in excised kidneys.[9, 13] The influence of 5-hydroxytryptamine warrants further investigation, but our preliminary results indicate,

*The extrarespiratory functions of this organ are still being discovered; it is therefore hazardous to assume that a kidney in a pump-lung system is "isolated."

from a large sampling, that, after as little as 15 minutes of perfusion, all of the whole-blood 5-hydroxytryphamine was free in the plasma, in accordance with the fact that all platelets had disappeared from the blood by this time.

The vascular effects of pentobarbital anesthesia and of denervation were probably of little or no importance.[6, 7, 21]

Although humoral factors may have continued to depress blood flow during the slow decline in phases II and III, extravascular tissue water gain and consequent increase of tissue pressure almost certainly contributed to the increased vascular resistance. Richards and Plant[22] attributed the increase of renal volume after adrenalin-induced efferent arteriolar constriction to proximal vasodilatation. If efferent arteriolar vasoconstriction is maintained in the presence of a constant, normal arterial pressure, diffusion of fluid into the extravascular spaces would be expected. The presence of perivascular fluid accumulations was found histologically in all of the kidneys of Groups B and C; in these preparations, reduced plasma colloid osmotic pressure also was present to augment diffusion.

It is probable that the gain of tissue fluid completed a self-perpetuating cycle wherein decreased blood flow enhanced vascular and tissue anoxia, and thus increased vascular permeability and tissue pressure. In addition to the factors of vasoconstriction and increased tissue pressure, mechanical obstruction of minute vessels—(arterioles, venules, and glomerular capillaries)—by thrombi and sludged red cells was also implicated and was confirmed histologically in several of the kidneys.

The Effect of Isonatronic Sodium Chloride.—Eggleton, Pappenheimer, and Winton,[8] using their pump-lung kidney preparation, found that a given increase of arterial pressure produced a rise of creatinine clearance only one-sixth as great as an equivalent decrease of colloid osmotic pressure. They concluded that dilution by Ringer's solution increases urine flow because of "increased permeability to water of the glomerular membrane." No details were given with regard to changes of renal plasma flow. It is well known that in the intact dog, the renal plasma flow and glomerular filtration rate increase following the infusion of normal saline or Locke's solution. Smith concluded that this is "presumably an effect related to the expansion of the extracellular fluid."[25]

In the present perfused kidneys, saline infusion was followed by an increased renal blood flow, an increased creatinine clearance, and an increased creatinine filtration fraction.

In normal cat and dog kidneys, reduction of arterial hematocrit within the 30 to 50 range, when arterial pressure is constant, does not cause significant changes in flow, although such changes do occur in the perfused hindlimb. This so-called "renal autoregulation" of blood flow has been deftly explained by Pappenheimer and Kinter[20] in terms of their cell separation theory. They postulated that the energy for the intrarenal cell separation is supplied by the kinetic energy of the blood. When this energy is reduced by lowering the arterial pressure, cell separation decreases and the dynamic hematocrit of

intrarenal blood rises toward that of the arterial blood.[15] If kinetic energy is reduced by vasoconstriction, it would follow that cell separation would again decrease. In the perfused kidneys described, velocity was markedly reduced, presumably by vasoconstriction. If there was no cell separation, and thus no autoregulation of flow, the flow-hematocrit relation of these kidneys should resemble that of the perfused hindlimb more closely than that of the normal kidney; there should be no significant elevations of flow at constant arterial pressure when hematocrit is reduced in the 30 to 50 range. Precisely this effect was seen (Tables II and III). Because of uncontrollable variables, including degree of vasoconstriction, tissue pressure gain and brevity of steady-state periods, precise quantitative relationships between flow and hematocrit could not be defined.

Sodium and potassium, as well as numerous other blood solutes, are known to influence neuromuscular excitability; in the preparations where their concentrations were changed, the vascular smooth muscle may have been affected. However, the evidence strongly indicates that absolute plasma concentration of sodium, within the range of normal to twice normal, was not a significant factor. Because increases of blood flow were also observed after Locke's solution (containing all of the known major electrolytes of plasma), any effects on flow due to chemical change must have been due to dilution of a solute not present in this mixture.

The increased creatinine clearance* was due chiefly, of course, to the increase of renal plasma flow. However, it was undoubtedly related also to the considerable decrease of colloid osmotic pressure, as indicated by the X_2/X_1 ratio. The increase of creatinine filtration fraction is consistent with this premise. It is not possible from these data to decide whether changes also occurred in glomerular membrane permeability.

Despite such elevations of creatinine clearance and creatinine filtration fraction, the values did not fall into normal ranges. If it is true that juxtamedullary diversion was of no importance, certain other factors might be hypothecated to explain the low creatinine filtration fraction, including abnormal glomerular membrane permeability and increased tubular pressure.

The Tubular Function.—If cell separation did not occur, the tubules received abnormally high quantities of red cells. This effect could conceivably result in aberrations of tubular function. The low levels of creatinine urine/plasma ratio indicate that the tubular capacity for water reabsorption was markedly reduced. The experiment of Fig. 4 demonstrated the inverse relation between urine/plasma ratio and urine flow.

The response of such preparations to varying plasma concentrations of sodium and potassium, with regard to urine/plasma ratio adjustment, will be discussed in a separate report.

*Shannon and Winton[24] have demonstrated that, at urine plasma ratios below 40, the creatinine clearance is a valid indicator of glomerular filtration rate in the excised, perfused, pump-lung kidney.

SUMMARY AND CONCLUSIONS

By the method described, 18 excised dog kidneys were perfused in a siliconized glass and Tygon system, at a temperature of 25° C. Heparinized, oxygenated, autologous whole blood which was not passed through an animal lung was the perfusate. The objective was to determine the usefulness of this technique in kidney storage and to document some of the hemodynamic factors associated with failure of the preparations.

Using simple diluents, including normal saline and Locke's solution, it was possible to maintain urine production for periods of about 7 hours. Although it cannot be stated that abnormal function indicates inadequate viability for storage purposes, it is felt that these preparations can be improved upon with the aim of achieving survival for unlimited periods.

At least one vasoconstrictor agency is present in the system at the beginning of perfusion and is rapidly acting. Possible factors in the blood flow decline of phase I, as well as the slower decline of the two later phases, include humoral agents, hypothermia, increased tissue pressure, and vascular obstruction by clumped red cells and thrombi. The reduction of flow was apparently great enough to abolish cell separation and autoregulation of flow within the hematocrit range of 30 to 50. The increased creatinine filtration fraction occurring after saline dilution was probably principally due to the decrease of colloid osmotic pressure. There appeared to be a marked reduction of tubular capacity for water reabsorption.

Further inquiries into such preparations, including studies of performance under normal temperatures, are in progress.

We are especially grateful to Drs. F. D. Moore and G. J. Dammin for their valuable advice and encouragement. We are also indebted to Drs. A. C. Barger, J. R. Pappenheimer, and N. I. Gold for their criticisms of the manuscript. They are not responsible in any way for its deficiencies. Miss Margaret E. Drolette of the Biostatistics Department, Harvard School of Public Health, gave indispensable help with the statistical methods.

The work would have been impossible without the technical assistance of Margaret Ball, Geraldine Shohet, Roberta Bruck, and the technicians of Dr. Moore's laboratory.

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CARCINOMA OF SWEAT GLAND ORIGIN

Report of a Case of 30 Years' Duration With Autopsy Findings

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In 1944 an unusual case of malignant papillary cystadenoma of sweat gland origin with metastasis to the regional lymph nodes was reported by one of us.[1] During the succeeding 13 years the subject of that report was kept under observation, was treated for various manifestations of neoplasm on many occasions, and finally succumbed in October, 1957, 30 years after the onset of tumor. Autopsy was performed. Because of the infrequency of authenticated cases of metastatic carcinoma of sweat glands and because of the long duration of this fatal neoplasm, the patient's clinical history subsequent to the initial report and the autopsy findings are presented here.

CASE REPORT

A 31-year-old Hebrew man was first admitted to the Hospital of the University of Pennsylvania on May 13, 1942, with a painless, slowly growing mass on the radial aspect of the left wrist about 4 cm. proximal to the radial styloid. The lesion had first been noted 15 years previously following an accident in which a steel sled runner had passed over the wrist, without, however, producing serious injury. A snapshot of the patient taken at the age of 16 attests to the presence of a tumefaction of the left wrist at that time.

Attempts at excision in 1937 and 1940 were followed by local recurrence. In 1942 excision was attempted at the Hospital of the University of Pennsylvania, but the tumor was too extensive to permit complete removal. Roentgen studies at this time showed a large defect in the distal volar aspect of the radius. An epitrochlear lymph node was removed and found to contain tumor. Amputation was advised but refused.

By late 1943 the arm and the hand were markedly edematous and many nodules were palpable in the scarred area on the radial aspect of the forearm. On Dec. 13, 1943, amputation was performed just distal to the deltoid insertion, but above the upper limits of the edema. Examination of the amputated arm showed a large tumor mass invading and destroying all the soft tissues of the dorsal part of the distal 12 cm. of the forearm, involving to a limited degree the radial aspect of the palmar surface. The distal 4 cm. of the radius was destroyed by tumor, but the ulna was not invaded. A mass of similar tumor tissue was found in the operative scar in the epitrochlear region. It was at this point in the evolution of the disease that the case was initially reported.

The patient was symptom free until October, 1946, when he complained of low back pain which radiated along the medial aspect of the left leg to the toes. This was accompanied by paresthesias along the outer aspect of the right thigh. A roentgenogram revealed a destructive lesion of the fifth lumbar vertebra, which was treated by radiation therapy at

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another institution. In 1946, 1947, and 1949 tumor nodules were excised from the left shoulder region and, finally, in 1951, a left thoracoscapular disarticulation was performed. Radiation therapy was given to the left shoulder region postoperatively.

Pain in the lumbosacral region with sciatic nerve radiation recurred repeatedly between 1946 and the patient's death in 1957. Three additional courses of radiation therapy totaling 4,700 r. in air were given to the lumbosacral region between May, 1954, and July, 1957. Lumbar laminectomies were performed by Dr. Robert A. Groff in August, 1954, and again in August, 1956. At both of these procedures epidural tumor was found to be causing compression of the nerve roots.

In November, 1954, the patient noted pain in the early morning hours over the posterior aspect of the lower ribs. A roentgenogram showed destruction of the pedicle of the twelfth dorsal vertebra and the adjacent head of the twelfth right rib. In addition multiple small densities were noted throughout the entire left lung field. He was treated with external irradiation, receiving 2,000 r. to the thoracic and lumbar spine and 600 r. to the lower right posterior chest.

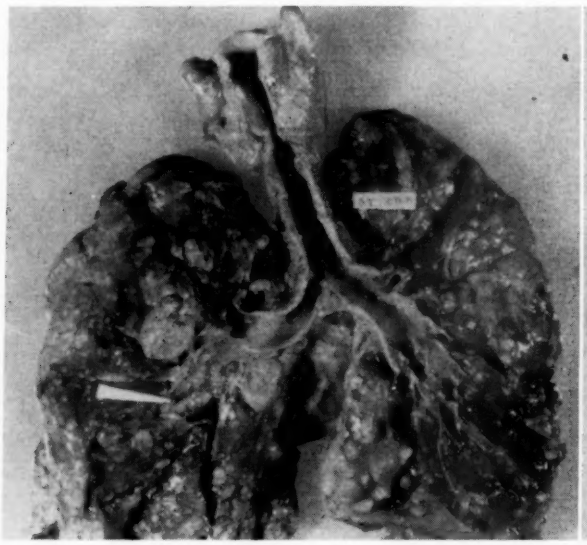


Fig. 1.

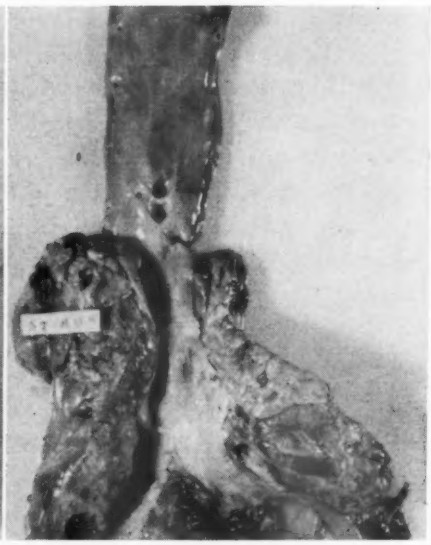


Fig. 2.

Fig. 1.—Metastases distributed diffusely throughout both lungs.
Fig. 2.—Tumor-containing lymph nodes surrounding the lower abdominal aorta and the common iliac arteries.

He was next seen in September, 1955, complaining of incapacitating pain in the left hip which radiated down the outer aspect of the left thigh. A roentgenogram showed osteolytic changes in both femoral shafts. Relief from pain followed radiation therapy to the upper portion of the left femur (3,000 r.) but no objective evidence of tumor regression was noted.

Chemotherapeutic measures including nitrogen mustard in April, 1957, triethylene melamine in May, and triethylene thiophosphoramide (TEPA) in September and October, 1957, were taken without any noteworthy effect.

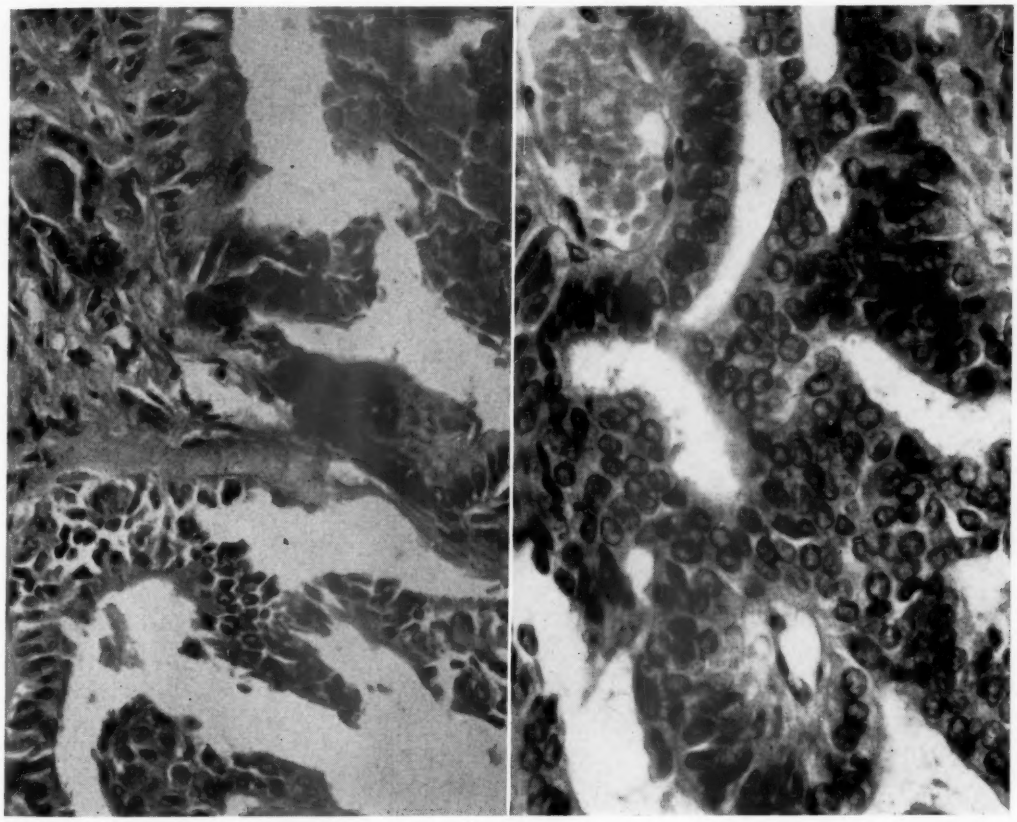
In October, 1957, he developed a febrile illness and was admitted to the hospital for the twelfth and final time on October 29. He was severely dyspneic and had a temperature of 107.2° F. The following morning he expired abruptly while a thoracentesis was being attempted.

AUTOPSY FINDINGS

Widespread tumor constituted the principal autopsy findings. Multiple tumor nodules, measuring up to 3 cm. in diameter, were present in the skin of

the left side of the chest and in both pleural cavities. Smaller nodules involved the epicardium. The lungs contained many metastases, measuring up to 4 cm. in diameter (Fig. 1). The mediastinal, retroperitoneal, and pelvic lymph nodes were converted into huge, matted tumor masses (Fig. 2). The epicardium, thoracolumbar spine, pelvis, and many ribs were other sites of metastasis. These were the only skeletal areas examined.

Other important findings included extensive bilateral bronchiectasis, presumed secondary to the pulmonary metastases, and multiple sacral decubitus ulcers, attributed, in part at least, to the heavy radiation.



A. *B.*

Fig. 3.—Photomicrographs illustrating the glandular and cystic character of the tumor. *A*, from lumbar vertebrae (×280). *B*, mediastinal lymph node (×400).

Histologically the tumor was essentially similar throughout. It was composed of fairly uniform and regular columnar or cuboidal cells frequently lining well-formed gland spaces (Fig. 3). The latter commonly contained mucin. Some areas presented a distinct papillary configuration (Fig. 4) whereas, in others, there was a tendency toward the formation of solid sheets of epithelial cells (Fig. 5), at times even suggesting epidermoid differentiation. Calcospherites were scattered throughout. Pleomorphism was inconspicuous but many mitotic figures were seen. The tumor, as seen in the autopsy material, differed

Fig. 4.

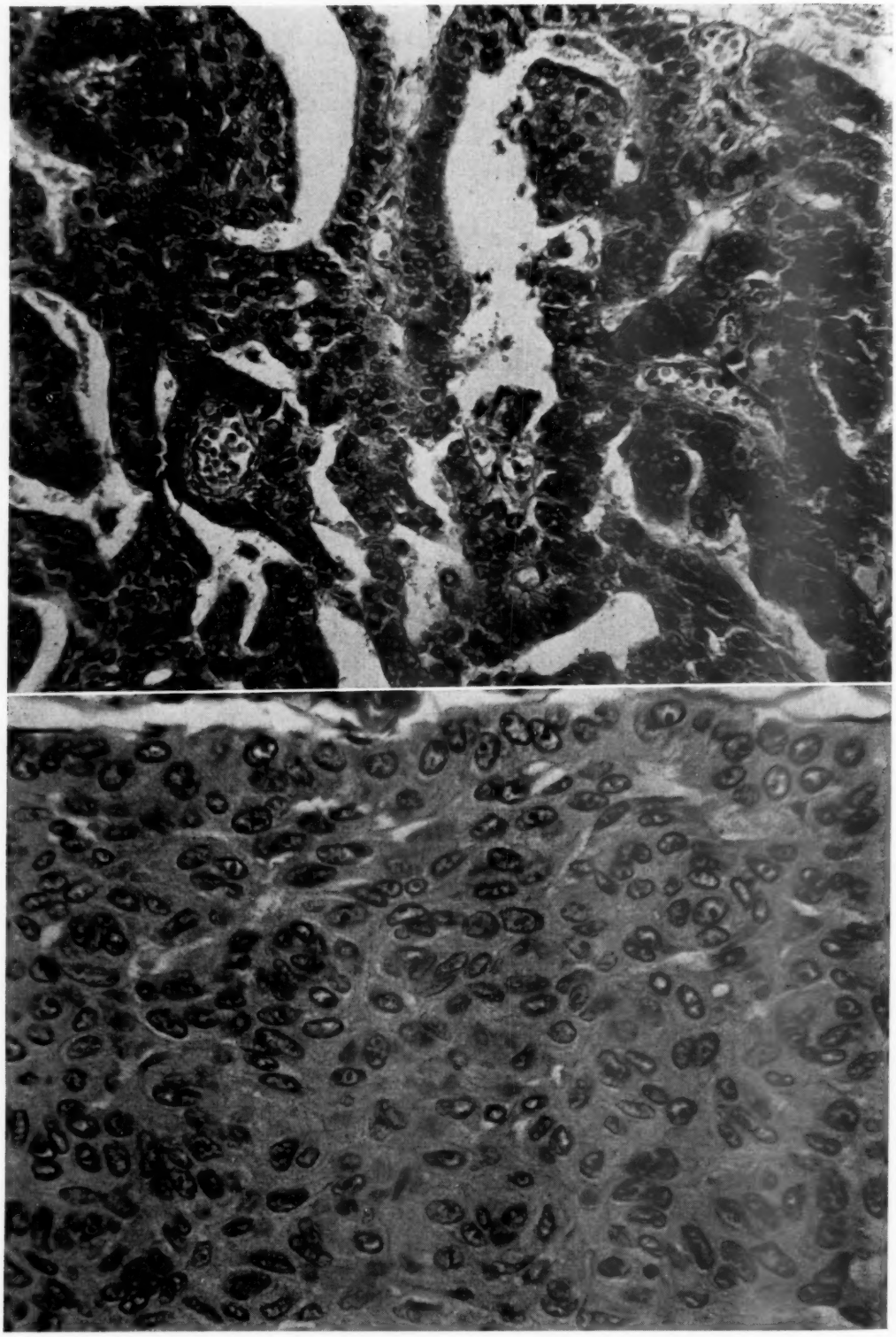


Fig. 5.

Fig. 4.—Lung metastasis demonstrating papillary configuration (×300).
Fig. 5.—Area of solid growth in mediastinal metastasis (×575).

from the earlier surgical material only in a lesser tendency toward cyst formation and papillary pattern and a slightly greater tendency toward growth in solid masses.

DISCUSSION

In recent reviews of the literature, Smith[4] and Teloh, Balkin, and Grier[7] emphasized the rarity of reports of authenticated cases of metastatic carcinoma of sweat gland origin, particularly with autopsy findings. Smith collected 21 cases in which there was convincing evidence of metastatic sweat gland carcinoma. Teloh, Balkin, and Grier's review listed only 14 of these cases but added 9 others, making a total, at least, of 31 cases recorded in the literature, including the case reported here. Eighteen of these cases had regional lymph-node metastasis and 13 had disseminated lesions. Autopsy findings in reported cases included metastases to lungs, pleura, liver, adrenal glands, ribs, pelvis, vertebrae, subcutaneous tissue, and thoracic, abdominal, and regional lymph nodes.

Stout and Cooley[5] note that the majority of the sweat gland carcinomas in their series were present in a quiescent state for a period of time before exhibiting infiltrative growth or metastasizing. Teloh, Balkin, and Grier[7] found the duration of the lesion in 18 cases to range from 2 months to 25 years with a median of 9 years and a mean of 10.7 years. In our case the tumor was first noted in the wrist in 1927, making the over-all known duration of the lesion 30 years. During the first 13 years of this period the tumor remained local. However, its malignancy during at least part of this period is attested to by the local recurrences following excisions in 1937 and 1940. Metastasis was first suggested by axillary and epitrochlear lymph-node enlargement following the second excision in 1940.

A definite diagnosis of malignancy was not made until 1942, and shortly thereafter regional node metastasis was proved by epitrochlear lymph-node biopsy. All of the surgical specimens removed at the Hospital of the University of Pennsylvania were characterized by cystic structures lined by orderly cuboidal epithelium with varying sized intraluminal papillary epithelial proliferations. This histologic pattern is still apparent throughout the widespread metastatic tumor found at autopsy although the tumor as a whole is slightly less differentiated. The tendency for sweat gland tumors to remain well differentiated has previously been noted by other authors, most recently by Teloh.[6]

The problem of differentiating benign from malignant sweat gland tumors has been pointed out by Stout and Cooley,[5] Keasbey and Hadley,[3] and Teloh.[6] Since these tumors are usually well differentiated, definite evidence of local invasion or metastasis appears to be the only reliable criterion of malignancy, although, for small lesions limited to the subcutaneous tissue, invasion may be difficult to prove. Local recurrence following excision should make one consider the diagnosis of carcinoma seriously, regardless of histologic appearance.

The importance of adequate surgery at the earliest possible time is emphasized by the reported case; it seems reasonable to suppose that amputation in

1940 or even 1942 might have resulted in cure. Although sweat gland tumors are characteristically slow growing, the potentiality for wide systemic spread is noted in this as well as other cases.

The patient received extensive radiation therapy, in particular to the lumbosacral region, where the total dosage was more than 4,700 r. Although symptomatic relief in treated areas was noted, there was no objective evidence of radiation effective at any time. Viable tumor was present in the lumbosacral region at autopsy and it seems fair to conclude that this sweat gland carcinoma was refractory to radiation therapy.

SUMMARY

The clinical history and autopsy findings are presented of a case of sweat gland carcinoma of the wrist first reported in 1944. Despite multiple attempts at surgical excision of the tumor, the patient developed widespread metastases and died of his disease. The over-all known duration of the neoplasm was 30 years. Throughout this period the tumor maintained an orderly intracystic papillary pattern. The tendency of carcinoma of sweat gland origin to be well differentiated and to grow slowly makes it a particularly insidious type of neoplasm.

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MASTECTOMIES WITH SIMULTANEOUS RECONSTRUCTION OF BREASTS

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WHEN the breasts are amputated for diffuse or reappearing benign disease, the patients are often subjected to severe psychologic trauma. Especially on younger women, the loss of one or both breasts should be considered as a serious mutilation.

To remedy such deformity following mastectomies and to provide desirable mammary eminence, one or multiple stage operations can be performed. Such operations have been accomplished by the introduction of gluteal fat tissue into the defects after the removal of the gland.[1, 4] After such procedures the immediate results were good. The late results were not very satisfactory due to absorption and induration of the freely transplanted tissues; also, gluteal scarring was produced. The rebuilding of flat breasts or postmastectomy defects was more satisfactory with derma-fat pedicle flaps[3, 5, 6] and free transplantation of the nipple[8] in large pendulous breasts after mammectomies.

The foreign body implants (Ivalon) are promising, but, because of complications, such as hardening, expulsion, and especially the yet unknown possible late deleterious results, many surgeons are hesitant in using them.

To embody all that was learned by previous experiences, a one-stage operation was developed. It excludes the free transplantation of tissues or nipples; simply utilizing local tissues for simultaneous rebuilding the breasts and preserving the blood supply to the transposed nipple allow a satisfactory one-stage mammary reconstruction which is as follows.[7]

OPERATIVE TECHNIQUE

1. The line of incision is marked at the lower lateral quadrant of the breast circumscribing the areola at its one-half to two-thirds lateral portion, preserving an adequate blood supply at its medial portion (Fig. 1, *A*).

2. A truncated conical sector is outlined at the lower outer quadrant of the breast* from which this, the epithelium, is removed by the dermatome or by a scalpel, preparatory to the development of a derma-fat pedicle flap (Fig. 1, *B*).

3. The incision is then deepened through the dermal and fat layers of the breast and raised from the glandular tissue, carefully preserving all fat and its blood supply at its base (Fig. 1, *C* and *D*).

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*With further experiences since an earlier publication,[7] we have changed the line of incision from the lower quadrant to the lower lateral portion of the breast, which results in less scarring below the breast and easier rotation of the nipple.

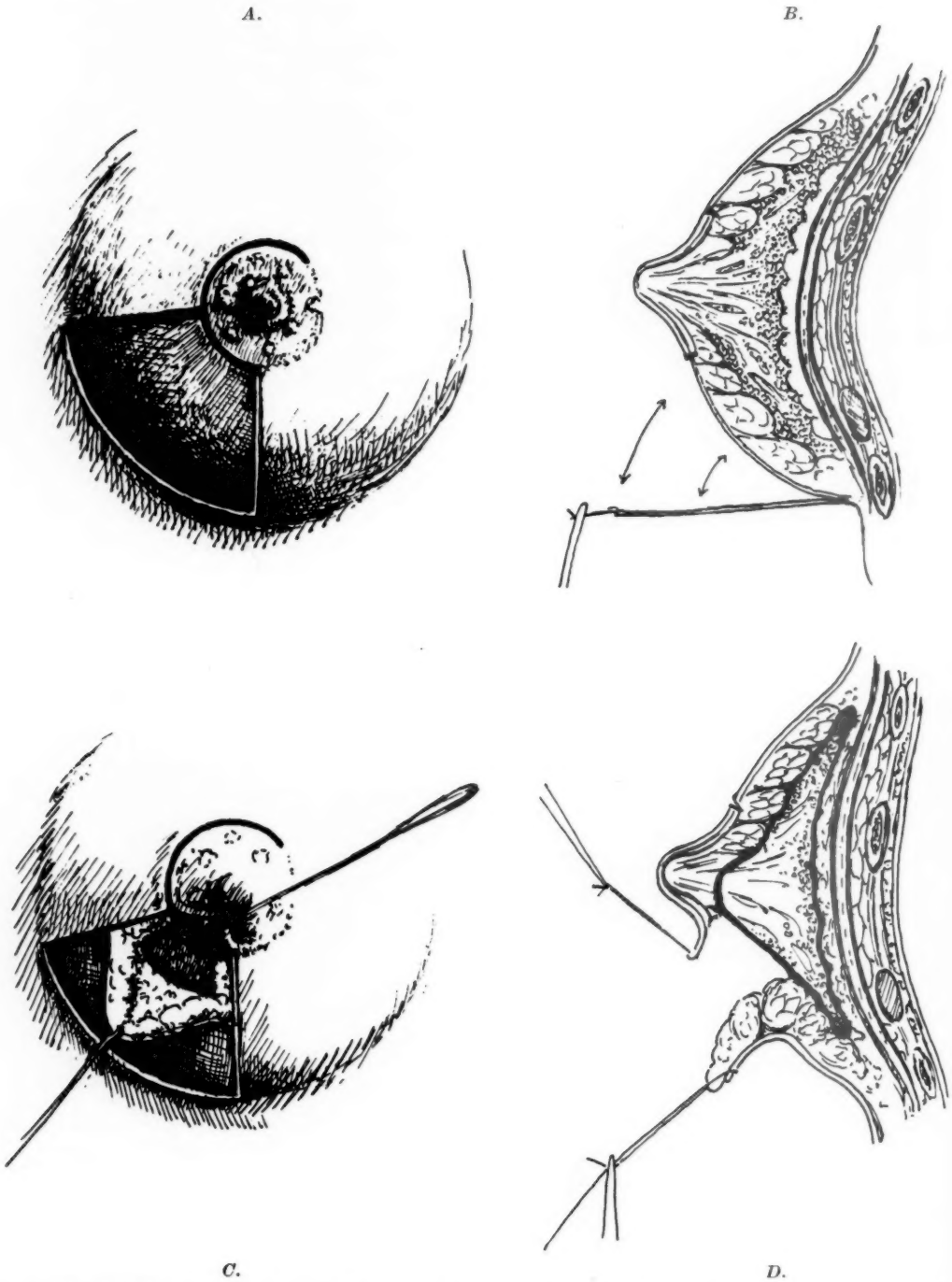


Fig. 1.—*A*, Drawing shows the line of incision around the nipple of the right breast and the area from which the epithelium was removed leaving the derma. *B*, Cross section of right breast showing skin, subcutaneous fat tissue, and gland. Arrows indicate the area from which the epithelium was removed. *C*, Development of the derma-fat pedicle flap carefully dissected from glandular tissue. *D*, Cross section showing derma-fat flap being developed, leaving glandular tissue marked with thick line. Subcutaneous tissues carefully preserved to increase volume of the newly formed breast.

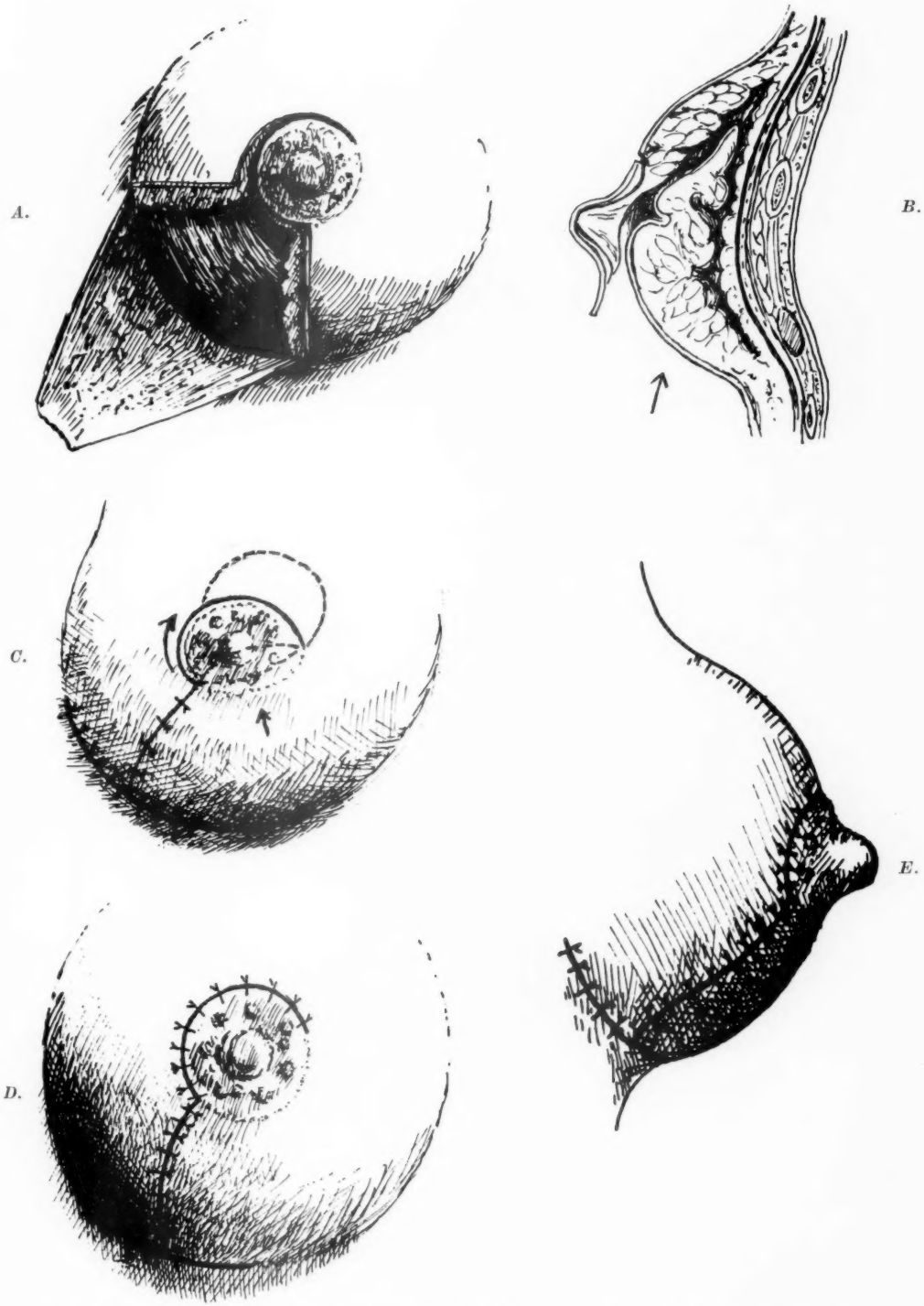
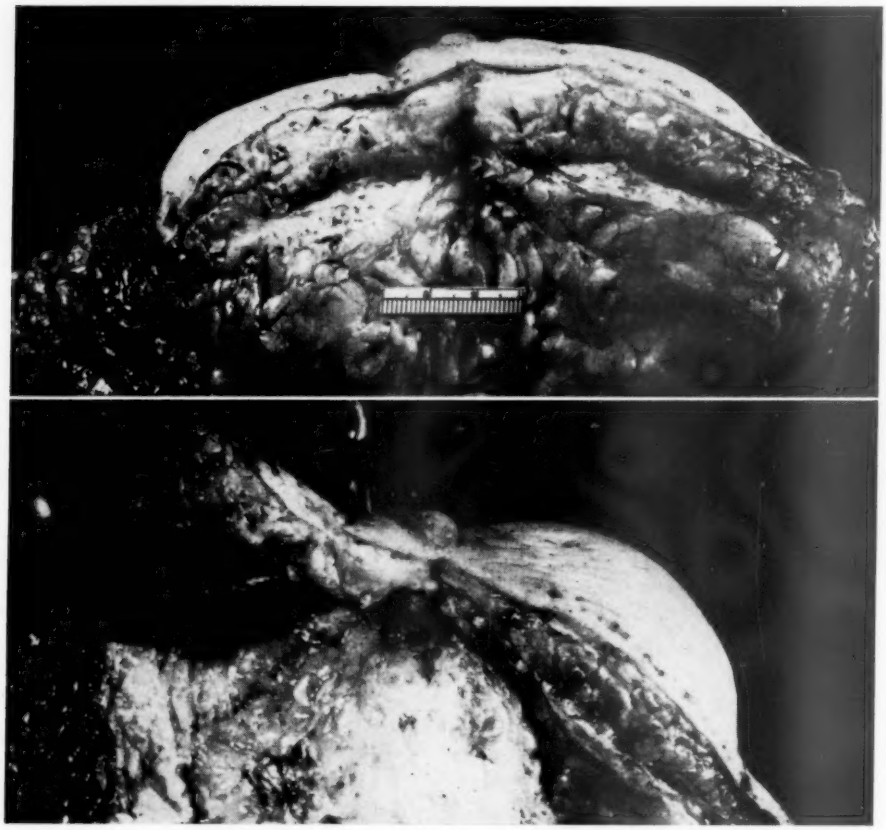


Fig. 2.—*A*, Pedicled derma-fat flap developed, glandular tissue excised. *B*, Cross section showing derma-fat pedicle introduced into the defect after removal of gland. *C*, Wound sutured over derma-fat flap which is possible through elasticity of the tissues, leaving suture line about 8 o'clock of breast in shape of inverted T. *D*, The nipple sutured with interrupted fine (-5-6-0) Dermalon sutures. The nipple pedicle rotated into its ideal place. A disc-shaped piece of skin corresponding to the size of the nipple is excised. *E*, Side view of newly formed breast showing suture line.

4. All glandular tissue is removed by sharp dissection, carefully preserving all subcutaneous fatty tissue in order to increase the volume of the newly formed breast. All axillary and subclavicular portions of the mammary gland tissue are removed to prevent recurrence of disease (Fig. 2, *A*).

5. After thorough hemostasis the derma-fat pedicle flap is introduced into the defect and, if necessary, fixed to the pectoral fascia and molded to form the core of the future breast (Fig. 2, *B*).

A.

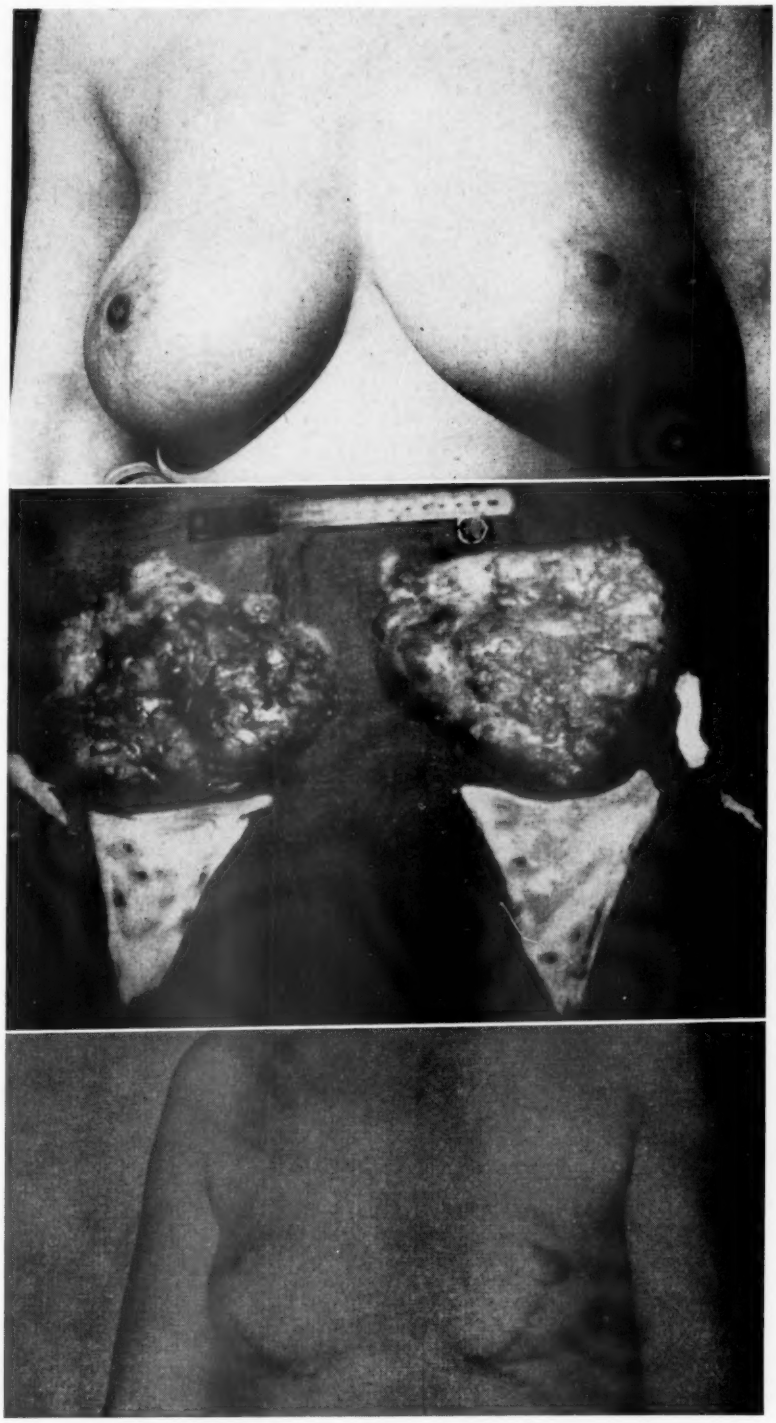


B.

Fig. 3.—*A*, Specimen of an amputated, newly formed breast, after 2 weeks. In one of our patients a radical operation was necessary for cancer (2 mm. in diameter) which was accidentally discovered during a thorough pathologic examination of the breast tissue removed for cystic disease. Upper portion shows the subcutaneous fat tissue layer which became thicker, through elasticity, when the newly formed breast was reduced. It also shows derma-fat layer folded into the defect to form the core of the breast. *B*, Separation of subcutaneous fat and the introduced derma-fat layer was rather difficult due to intensive scarring. There was no cyst formation or foreign-body reactions; healing was undisturbed.

6. The skin is fitted over the derma-fat cone; the lateral corner is gently undermined to facilitate closure and to obtain a desirable form. The skin is sutured with fine nonabsorbable Dermalon sutures. Redundant skin areas are smoothed by excisions.

7. The nipple pedicle is now rotated into its "ideal" position; a skin-disc is excised to receive the nipple (Fig. 2, *C*) which is sutured into place by fine nonabsorbable interrupted sutures. If a skinfold is formed after rotation of

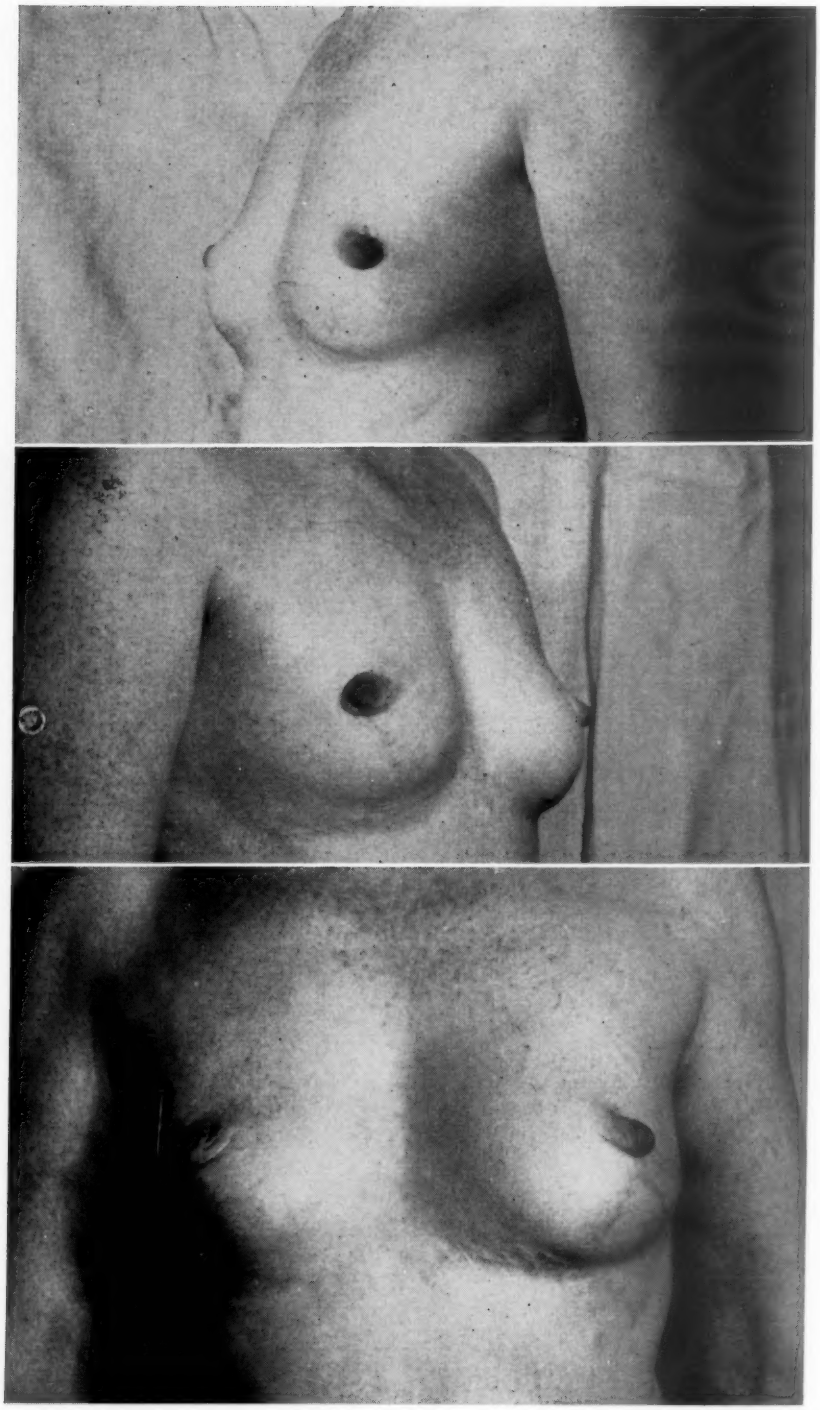


A.

B.

C.

Fig. 4, *A*, *B*, and *C*.—*A*, Reappearing fibrocystic disease of both breasts. (Amputation was advised elsewhere.) *B*, Specimen of completely excised breast shows numerous cysts, also the size of excised epithelium in preparation of derma-fat pedicle flap. *C*, Immediate postoperative result.



D.

E.

F.

Fig. 4, *D*, *E*, and *F*.—Same patient 4 years later. Scars have faded, breast retained original shape and size, feels soft and normal. Nipples erectile.

the nipple at its superior portion, it may be corrected by removing the epithelium over a triangular area and infolding the denuded derma. A smooth surface is obtained with the preservation of the necessary blood supply of the nipple (Fig. 2, *D*).

A rubber drain, inserted, is removed in 48 hours. A satisfactory immobilization is obtained by using a 12-inch-wide bandage, "fashioned" by twisting as it is applied to the chest.

Early ambulation is recommended. Sutures are removed progressively within 4 to 14 days.

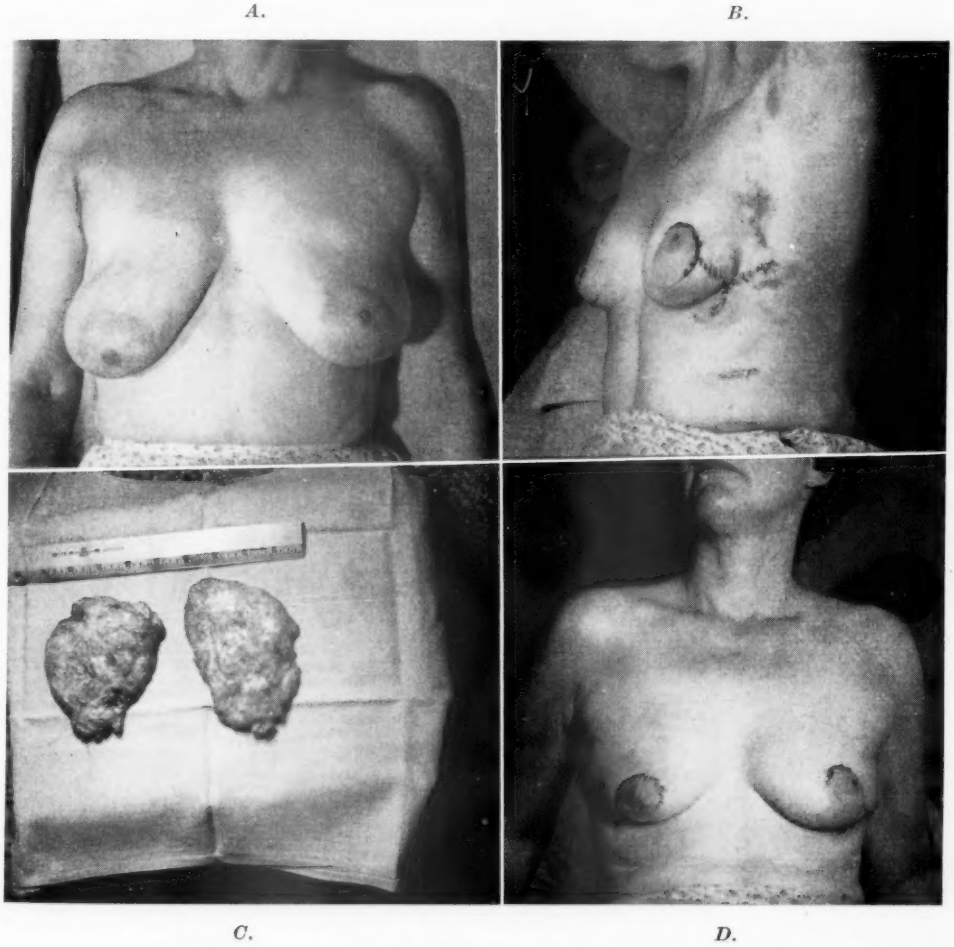


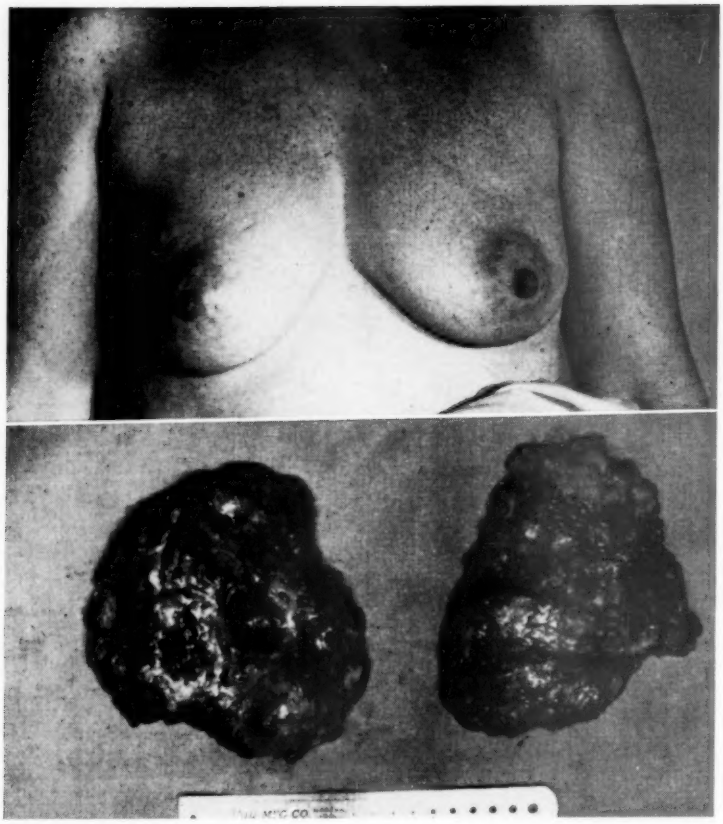
Fig. 5.—*A*, Deformed breasts after 2 operations for multiple cysts reappearing within 2 years. Photographed before complete excision of glands. *B*, Lateral view showing suture line. *C*, Specimen of fibrocystic disease. *D*, Postoperative result.

COMMENTS

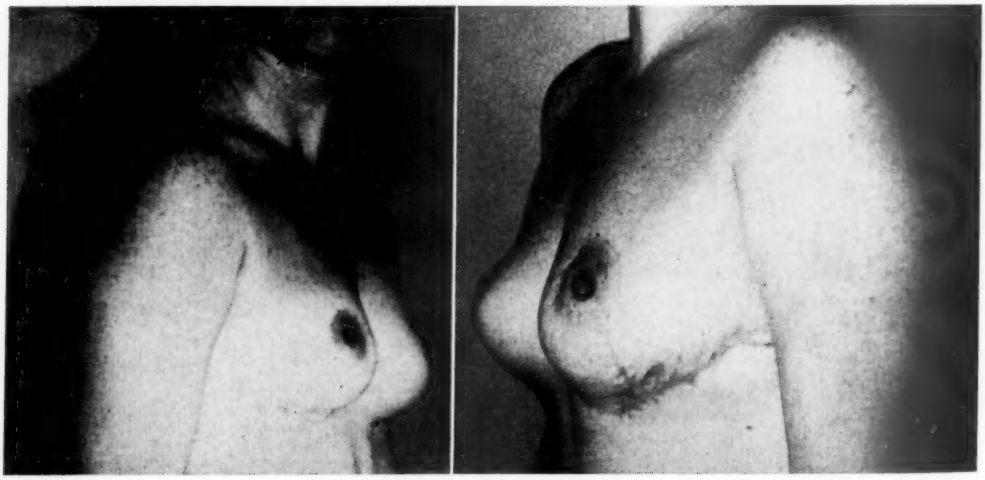
There was no mortality nor morbidity, with the exception of one hematoma, due to occlusion of the drain in one patient. It was absorbed without drainage and healed without further complication. There was no total or partial necrosis of nipples.

Follow-up examinations of all the 12 reconstructed breasts from 1 to 4 years disclosed that: The newly formed breasts retained their original shape,

A.



B.



C. *D.*

Fig. 6.—*A*, Reappearing fibrocystic disease of both breasts. *B*, Completely removed glandular tissues from breasts. *C* and *D*, Three years later. Breasts feel normal and have maintained their original shape and soft consistency.

size, and consistency. The nipples preserved their original size and remained erectile, their sensibility returning within 3 months after operations. The newly formed breasts feel normal to the patients and are soft to the palpating finger. It remains a "finished product" after a one-stage operation due to the fact that the original blood supply of all tissues was preserved.

Although this operation seems to be very satisfactory for the average sized breasts, it is less so if the breasts are rather small, as in the very thin individual, since there is not enough subcutaneous tissue to increase sufficiently the bulk of the newly formed breast, nor does the derma-fat provide sufficient material if a larger breast is desired.

Pendulous hypertrophic breasts, with wide areolas, are also less suitable for this operation unless a secondary correction is contemplated.

The extremely low location of the nipple in pendulous breasts is also less favorable for the uplift and rotation. In such cases the utilization of derma-fat flaps with free transplantation of nipples is desirable.

INDICATIONS AND CONTRAINDICATIONS

Surgeons familiar with the described technique will find increasing numbers of indications to remove the diseased mammary gland. The plastic surgeon will also find this operation applicable in mastoplasties with diseased glandular tissues.

This procedure aims to replace all simple mastectomies for benign mastopathies, such as bilateral cystic disease.

The only contraindication is the presence of malignant tumors when a radical operation is imperative.

SUMMARY

To replace simple mutilating mastectomies, a one-stage operation is presented for the complete reconstruction of a normal-appearing breast, utilizing local tissues, after the complete removal of all of the mammary glands.

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STORAGE OF BLOOD FOR OPEN HEART OPERATIONS

Experimental and Clinical Observations

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RECENT developments in open heart operations in which extracorporeal circulation is utilized for temporary cardiopulmonary bypass have introduced complicated hematologic problems and placed an increased burden on blood banking facilities. The facts that blood for priming the pump-oxygenator and for use in the extracorporeal system must be freshly drawn, heparinized, and used at approximately body temperature introduce difficulties in procurement and storage that are not encountered in other surgical procedures. Heparinized blood is necessary because citrated blood, when perfused rapidly during cardiac bypass, produces serious cardiac disturbances, such as ventricular fibrillation. Because of the possibility of deterioration of the components of stored blood, when the project of cardiopulmonary bypass was first undertaken, only blood drawn 2 to 4 hours before operation was considered suitable for use in the pump-oxygenator. The blood was maintained at body temperature until it was to be used. Thus, collection of blood was begun at 7:00 A.M. for an operation scheduled at 11:00 A.M. Blood was drawn into 500 c.c. siliconized bottles containing 30 c.c. of physiologic saline and 15 mg. of heparin. This method of procurement proved both inconvenient and impractical. Consequently, operations were often delayed several hours, particularly on days when more than one operation was scheduled.

As the number of these operations performed increased in frequency, it became obvious that these limitations on procurement and storage of blood had to be eased if the program were to continue at such a pace. Consequently, efforts were directed toward development of a safe and effective method of procurement of blood on the day before operation with storage until the time of operation. A method of procurement and storage of blood was devised which has proved satisfactory in more than 300 operations performed with use of the pump-oxygenator during the past 2 years. Experimental evidence supporting the efficacy of this method will be presented.

Since blood collected in saline solution and heparin cannot be preserved for more than a few hours without dextrose, a preservative anticoagulant solution

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TABLE I. DAILY HEMOGRAM STUDIES OF BLOOD DRAWN IN 60 C.C. OF GLUCOSE AND PHYSIOLOGIC SALINE AND CONTAINING 25 MG. OF HEPARIN

	DATE OF DRAWING									
BAG NO. 4623	SEPT. 19, 1956	SEPT. 20, 1956	SEPT. 21, 1956	SEPT. 24, 1956	SEPT. 25, 1956	SEPT. 26, 1956	SEPT. 28, 1956	OCT. 1, 1956	OCT. 3, 1956	OCT. 5, 1956
Hemoglobin	13.9	13.0	12.8	13.0	12.5	13.7	12.3	11.4	12.1	12.7
Plasma hemoglobin	0.23	0.3	0.5	0.1	0.2	0.3	0.3	0	0.2	0.1
Hematocrit	42	41	66	41	41	45	39	37	39	38
Platelets	162,000	124,000	124,000	24,000	22,000	18,000	16,000	4,000	0	0
Osmotic fragility	32-44	36-44	34-46	32-46	36-46	36-46	36-48	40-48	48-38	Not done
Mechanical fragility										
Hemoglobin	12.5	12.8	20.0	12.8	12.5	13.9	12.3	11.3	12.3	12.5
Plasma hemoglobin	0.53	0.4	0.8	0.2	0.1	0.2	0.1	0.1	0.2	0.4
Hematocrit	40	40	64	39	40	45	39	37	39	37

consisting of 60 c.c. of a 5 per cent solution of dextrose in physiologic saline solution and 25 mg. of heparin was prepared for each 500 c.c. of blood to be collected. Before this solution was employed clinically, a number of experimental observations was made at daily intervals on the blood, which was stored at 4° C. In Tables I and II are shown the results of these studies, which indicate no decrease in the hemoglobin or hematocrit values during the first several days. Platelets were present in normal numbers for 3 days but rapidly disappeared during the next few days with complete disappearance by the ninth day. These results are similar to those obtained with blood preserved in A.C.D. solution. Results of osmotic and mechanical erythrocyte fragility tests were within normal limits during the first 10 days of testing but subsequent values gradually increased. The plasma hemoglobin value showed no increase during the testing period. In addition other studies indicated that the oxygen absorption by stored blood at the end of 24 hours was approximately normal.

TABLE II. DAILY HEMOGRAM BEGINNING ON FOURTH DAY AFTER DRAWING OF BLOOD PROCURED IN PLASTIC BAG CONTAINING 60 C.C. OF 5 PER CENT GLUCOSE IN PHYSIOLOGIC SALINE AND 25 MG. OF HEPARIN

BAG NO. 4678 SEPT. 20, 1956	DATE OF DRAWING						
	SEPT. 24, 1956	SEPT. 25, 1956	SEPT. 26, 1956	SEPT. 28, 1956	OCT. 1, 1956	OCT. 3, 1956	OCT. 5, 1956
Hemoglobin	12.7	12.7	14.4	13.9	12.5	13.5	14.2
Plasma hemoglobin	0.0	0.1	0.4	0.1	0.1	0.4	0.2
Hematocrit	44	44	47	44	43	44	44
Platelets	36,000	40,000	28,000	34,000	12,000	6,000	6,000
Osmotic fragility	38-46	36-48	40-50	38-50	36-50	50-44	Not Done
Mechanical fragility							
Hemoglobin	13.0	12.7	14.3	14.0	12.5	13.4	14.3
Plasma hemoglobin	0.2	0.2	0.2	0.1	0.3	0.4	0.8
Hematocrit	43	43	46	43	41	43	43

Encouraged by these results, we established the following program for procurement and preservation of blood, which, after substantiation by other laboratory and clinical studies, was adopted for all such operations.

METHOD OF PROCUREMENT AND PROCESSING

I. Procurement.—

A. Donor procurement:

1. Donors are obtained from the professional donor list of the central community blood bank.*
   a. Donors have been previously ABO grouped and Rh typed (CDE slide method).
   b. Donors have fasted at least 4 hours prior to drawing.

B. Donor processing:

1. History of previous disease is reviewed.
2. Routine hemoglobin count is obtained by the copper sulfate technique.
3. Blood pressure, temperature, and pulse rate are recorded.

C. Blood collection (drawn the afternoon before operation):

1. Fresh A.C.D. blood for use in immediate postperfusion period (usually 2 to 3 units).

*Southwest Blood Banks Inc., Houston, Texas.

a. Blood drawn in A.C.D. solution according to regulations of National Institutes of Health.
b. After blood is drawn:
(1) VDRL* serology is done.
(2) It is rechecked for ABO group, back grouped, Rh typed (CDE), and back typed.
(3) It is placed in refrigerator (4° C.) and cross-match is performed.

2. Collection of fresh heparinized blood:
a. Solution used per unit of blood collected is (25 mg. heparin in 60 c.c. of 5 per cent solution of glucose in physiologic saline in plastic bag† or in silicone-coated bottle).
b. Method of collection:
(1) Silicone-coated needles and plastic disposable tubing are used throughout.
(2) Blood is drawn by gravity method, care being exercised to prevent cellular damage and coagulation.
c. Blood is refrigerated immediately after collection.
d. Blood is cross-matched after collection, not before.
e. Blood is grouped (ABO) and typed (Rh). If Rh negative D^u determination is performed, the blood is back grouped and typed.
f. VDRL serology is performed.
3. All blood drawn the afternoon before is processed immediately and placed in refrigerator.
4. Thirty minutes before operation all blood in A.C.D. and heparin solutions are placed in the 37° C. water bath. Blood should not be overheated and warming period should not exceed one hour.

II. Cross-Matching Procedure for Open Heart Operations.—

A. Grouping and typing:
1. Blood of donor and patient is grouped (ABO); slide method is used and directions of the antiserum manufacturers are followed exactly.
2. Blood is back grouped, known A and B cells being used.
3. Blood is Rh typed against CDE (anti-Rh) by slide method.
4. Blood is back typed, known CDE cells being used.
5. Usual care is exercised in labeling and following manufacturers' directions.
6. Blood is checked for D^u according to standard methods.
7. Albumin controls are set up with Rh typing.

B. Cross-match procedure:
1. Saline cross-match is carried out by routine method between patient and donor (major and minor).
2. Coombs cross-match is performed between patient and donor.
3. Saline and Coombs type cross-matches are done between pooled donor cells (a pool of all donors) and patient.
4. If question exists after reading the Coombs cross-match, the tubes are incubated for one hour.

EXPERIMENTAL METHOD

The following methods were used to study blood from patient and pump during and after extracorporeal circulation.

*Venereal Disease Research Laboratory test.
†Kindly supplied by Abbott Laboratories, Scientific Division, North Chicago, Ill.

1. Blood samples for biochemical determinations were drawn at intervals of approximately 2 minutes from a T tube inserted in the arterial and venous connections of the pump and from the patient's antecubital vein in the postoperative period.

2. Erythrocyte osmotic fragility was determined; the usual concentration of saline and normal control was used.

3. Erythrocyte mechanical fragility was determined by the method of shaking with glass beads and measuring resultant plasma hemoglobin using standard control.

4. Blood pH was determined by standard technique with a Beckman Model G pH meter with constant temperature blood pH electrode.

5. CO_2 content was determined by the manometric method of Van Slyke.

6. Blood O_2 saturation was determined by Waters-Connelly direct reading oximeter.

7. Serum chloride was determined by the method of Schales and Schales.

8. Serum sodium and potassium was determined by the Beckman Clinical Model flame photometer.

9. Blood and plasma hemoglobin were determined by the cyanomethemoglobin method.

10. Blood glucose was determined by the method of Benedict. If any question existed regarding sterility of the blood, each bag or bottle was cultured for aerobic and anaerobic bacteria.

RESULTS OF EXPERIMENTAL STUDY

These studies indicated that the pH of the blood from the arterial and venous sides of the pump varied from start to finish of the extracorporeal circulation. The pH tended to increase slightly during extracorporeal circulation and decrease moderately in the immediate postoperative period, returning to normal in 6 to 8 hours after operation. This pH drop did not appear to affect the patient's condition. In Tables III, IV, and VI are typical studies on several patients showing a pH variation during perfusion and in the immediate postoperative period. All patients recovered uneventfully. In one of the patients (Table IV) the pH showed a maximum of 7.66 during the period of extracorporeal circulation and gradually fell to 7.20 six hours postoperatively. The CO_2 content did not change. Lactic acid determinations were not done. A similar decrease in pH was observed in other patients during the first 6 hours after extrathoracic operations. Thus, this phenomenon has not been adequately explained, but apparently the state of temporary acidosis is unrelated to the method of drawing or storing blood. Acidosis is probably secondary to poor respiratory exchange in the postanesthetic period and also to the magnitude of the surgical procedure. No appreciable change in osmotic or mechanical fragility was demonstrated in samples of blood taken from the extracorporeal pump (Table V). Carbon dioxide determinations performed on blood samples removed from the pump revealed no significant change during the perfusion or in the immediate postoperative period (Tables III, IV, and VI).

A number of isolated studies were performed on the stored blood. In Table VII is demonstrated the progressive loss of glucose in the preserved blood during 27 hours of incubation at 37° C. The pH decreased from 7.10 to 7.00 while the glucose content dropped from 556 mg. per cent to 380 mg.

TABLE III. pH, CO_2, pCO_2, O_2 SATURATION AND PLASMA HEMOGLOBIN STUDIES ON BLOOD TAKEN FROM THE ARTERIAL AND VENOUS CONNECTIONS OF PUMP AT APPROXIMATELY 2 MINUTE INTERVALS DURING CARDIOPULMONARY BYPASS AND FROM THE ANTECUBITAL VEIN IN THE IMMEDIATE POSTOPERATIVE PERIOD

	VENOUS SIDE				ARTERIAL SIDE				
PATIENT NUMBER	SAMPLE AT 2 MINUTE INTERVALS	PLASMA HEMOGLOBIN (GM. %)	pH	CO_2 (mEq.)	SAMPLE AT 2 MINUTE INTERVALS	pH	CO_2 (mEq.)	O_2 SATURATION (%)	P CO_2
Patient 1	V_1 (Control)		7.12	–	A_1 (Control)	7.28	12	98.0	25
	V_2		7.42	–	A_2	7.40	16	99.0	25
	V_3		7.40	–	A_3	7.48	17	99.0	23
	V_4		7.42	–	A_4	7.40	17	99.5	27
	V_5		7.37	–	A_5	7.39	16	100.0	26
	V_6		7.40	–	A_6	7.43	15	–	23
	V_7		7.39	–	A_7	7.48	–	–	–
	2 Postoperative		7.15	24					65
Patient 2	V_1	0.1	7.33	20	A_1	7.46			
	V_2	0.1	7.47	20	A_2	7.54			
	V_3	0.0	7.44	19	A_3	7.52			
	V_4	0.2	7.43	18	A_4	7.47			
	V_5	0.1	7.44	18	A_5	7.48			
	V_6		7.43	–	A_6	7.46			
Patient 3	V_1	0.35	7.58	19					
	V_2	0.3	7.51	18					
	V_3	0.3	7.53	18					
	V_4	0.3	7.55	18					
	V_5	0.3	7.55	18					
Patient 4	V_1	0.15	7.30	19					
	V_2	0.15	7.27	18					
	V_3	0.075	7.28	17					
	V_4	0.075	7.26	16					
Patient 5	V_1		7.49	19					
	V_2		7.47	18					
	V_3		7.32	18					
	V_4		7.35	18					
	V_5		7.32	18					
	V_6		7.28	18					
	V_7		7.20	16					
	V_8		7.32	18					
	V_9		7.27	17					
	V_{10}		7.23	18					
	V_{11}		7.23	19					
Patient 6	V_1		7.23	25					
	V_2		7.15	24					
	V_3		7.30	24					
	V_4		7.28	24					
	V_5		7.28	24					
	V_6		7.22	24					
	V_7			23					
	2 hr. post-operative		7.14	23					
	6 hr. post-operative		7.08						
	8 hr. post-operative		7.33						
Patient 7	V_1		7.20	18					
	V_2		7.33	17					
	V_3		7.30	18					
	V_4		7.24	18					
	6 hr. post-operative		7.13						
	8 hr. post-operative		7.19						

Blood for priming the pump was procured and processed more than 12 hours before operation.

per cent. Even with an apparent increase in glycolysis the pH did not fall significantly; this suggests that formation of lactic acid was insufficient to produce a more acid solution.

During the pumping procedure, variation in numbers of platelets was noted (Table VI). This observation was probably produced by dilution factors or

TABLE IV. pH AND CO_2 OF BLOOD FROM THE VENOUS CONNECTION OF PUMP DURING PERFUSION AND FROM THE ANTECUBITAL VEIN ON PATIENT IN THE IMMEDIATE POSTOPERATIVE PERIOD

PATIENT NUMBER	SAMPLE	pH	CO_2 (mEq.)
Patient 8	V_2 (at beginning of perfusion)	7.66	21
	2 hr. postoperative	7.29	21
	3½ hr. postoperative	7.26	21
	6 hr. postoperative	7.20	20
Patient 9	V_1 (at beginning of perfusion)	7.32	
	V_2 (2 min. later)	7.30	
	3 hr. postoperative	7.32	
	6 hr. postoperative	7.34	

Blood procured and processed more than 12 hours preoperatively.

TABLE V. PLASMA HEMOGLOBIN, MECHANICAL FRAGILITY, AND OSMOTIC FRAGILITY DETERMINATIONS ON BLOOD FROM THE VENOUS CONNECTION OF THE PUMP

SAMPLES FROM PATIENT 10	PLASMA HEMOGLOBIN (GM. %)	OSMOTIC FRAGILITY		MECHANICAL FRAGILITY OF PLASMA HEMOGLOBIN (GM. %)
		PER CENT SALINE BEGINNING HEMOLYSIS	PER CENT SALINE COMPLETE HEMOLYSIS	
V_1 (Control)	0.000	0.46	0.32	0.03
V_2	0.025	0.46	0.28	0.05
V_3	0.025	0.46	0.32	0.05
V_4	0.000	0.46	0.32	0.05
V_5	0.000	0.46	0.32	0.03
V_6	0.02	0.44	0.32	0.02
V_7	0.000	0.46	0.32	0.03

Blood procured and processed more than 12 hours preoperatively.

TABLE VI. pH, CO_2, PLASMA HEMOGLOBIN, AND PLATELET COUNTS ON BLOOD TAKEN FROM THE VENOUS CONNECTION OF THE PUMP AT 2 MINUTE INTERVALS DURING PERFUSION IN THE IMMEDIATE POSTOPERATIVE PERIOD

SAMPLES FROM PATIENT 11 AT 2 MINUTE INTERVALS	pH	CO_2	PLASMA HEMOGLOBIN	PLATELETS
V_1	7.33	23	0.0	102
V_2	7.32	23	0.1	190
V_3	7.32	23	0.0	146
V_4	7.35	23	0.0	102
V_5	7.37	23	0.1	86
V_6	7.36	23	0.0	48
V_7	7.32	23	0.0	36
V_8	7.31	23	0.1	80
V_9	7.30	22	0.1	60
V_{10}	7.28	21	0.1	57
V_{11}			0.0	242
4 hr. postoperative	7.23	16		
6 hr. postoperative	7.40	20		

Blood was procured and processed at least 12 hours preoperatively.

TABLE VII. INTERVAL pH AND BLOOD GLUCOSE CONTENT ON BLOOD PROCURED AND PROCESSED AT LEAST 12 HOURS PRIOR TO TESTING AND INCUBATED AT 37° C. FOR 8 HOURS

SAMPLE NUMBER	HOURS AFTER PROCUREMENT	INCUBATION TIME (HOURS)	pH	GLUCOSE
1	20	1	7.10	556
2	24	5	7.02	436
3	27	8	7.00	380

technical error rather than actual destruction of platelets since they recovered rather promptly at the end of the perfusion.

DISCUSSION

In the majority of more than 300 patients operated upon by us by cardiopulmonary bypass, the methods described for procurement and storage of blood were used. No major or minor hemolytic transfusion reactions occurred and no other major surgical complications developed that could be attributed to the methods by which the blood was secured. Daily postoperative hemograms revealed slight postoperative anemia, usually beginning on the second or third postoperative day, occasionally requiring subsequent transfusion. Whether this represents some delayed reaction to the method of procurement and storage of blood was not clear. Postoperative plasma hemoglobin determinations were usually less than 100 mg. per cent and no evidence of late erythrocytic destruction was found. Although in our early cases apparent hemorrhagic manifestations were occasionally encountered, no such complication has occurred in the last 100 patients. Improvements in methods of perfusion probably account for this favorable change. This complication cannot be attributed to hematologic factors. Unsatisfactory perfusion may produce capillary damage perhaps due to anoxemic changes and bleeding occurs as a result of this factor rather than the lack of some clotting factor in the blood. The use of fresh A.C.D. blood may be a deterring factor in control of hemorrhagic manifestations after operation.

SUMMARY

Procurement of blood for use in operations employing temporary cardiopulmonary bypass introduces special problems. Heparin must be used as the anticoagulant. Previously, blood was collected from professional donors immediately before operation. A study is presented in which blood was collected more than 12 hours preoperatively for convenience primarily in order to conform to a standard operative schedule and to facilitate the processing of blood. Physical, cytologic, and biochemical experimental observations on blood procured in this manner reveal the safety and efficacy of the technique. Results in more than 300 patients undergoing cardiopulmonary bypass indicate that the method is satisfactory for clinical application. The technique has permitted performance of multiple operations in a single day and promoted careful, unhurried processing of blood.

Additional studies are already in progress to determine if blood may be safely stored for 3 to 5 days using the solution described. The results of this study will be reported later.

DIGITAL AND INSTRUMENTAL COMMISSUROTOMY IN MITRAL STENOSIS

A Study of 2,000 Cases

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STENOSIS of the mitral valve induces well-known hemodynamic modifications which in turn are the cause of a well-defined clinical entity. The purpose of surgical treatment is to correct this anatomic defect. Numerous authors and specific anatomic conditions of the valve have resulted in many different technical modifications of the procedure.

We will not consider in this paper the problem of the route of approach to the valve because now there is complete agreement among the authors that the left auricular approach represents the simplest procedure unless in single cases particular difficulties exist. (In our department Professor A. M. Dogliotti has repeatedly entered the left atrium through a pulmonary vein or the atrial wall especially with a right thoracotomy as described by Bailey.)

To improve the over-all operative mortality and survival rate in the various groups of patients with mitral stenosis, we are particularly concerned with the problem of the choice of the method of dilating the valvular orifice, whether by finger fracture or by instrumental valvulotomy.

PURPOSE OF THE STUDY

The questions we would like to answer in this paper are:

1. When is the finger fracture technique alone sufficient to give good hemodynamic results?
2. In which anatomic conditions can satisfactory results be obtained with this technique?
3. If the finger fracture technique is to be used, what is the smallest orifice diameter which can be considered adequate?
4. Do repeated maneuvers with the finger, in order to obtain a larger orifice, represent a serious possibility of complications during the surgical intervention?
5. Which of the two commissures is preferable for finger fracture?
6. In which conditions must instrumental valvulotomy be preferred?
7. In which anatomic conditions is instrumental valvulotomy indicated?
8. Which of the two commissures is more convenient to incise?
9. What is the anatomic extent to which the instrumental incision has to be extended?

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10. Does instrumental valvulotomy represent a greater surgical risk than the finger fracture technique?

11. Which of the many instruments that have been described is the safest and most practical?

12. Can instrumental valvulotomy be used to further improve the result obtained by finger fracture?

13. From a statistical viewpoint, what is the frequency of complications with each of these methods?

14. What are the immediate results which can be obtained with either of the two methods?

MATERIAL AND METHOD

From 1951 to the date of the present study (May 1957), mitral commissurotomy has been performed on more than 2,500 patients by Professor A. M. Dogliotti and co-workers in the department of Cardiac Surgery of the University of Turin Medical School. From those patients operated upon, 2,000 subjects on whom complete clinical data and surgical findings were available have been chosen for the present study.

Since the beginning of mitral surgery we have adopted in this department a classification of mitral valvular pathology based upon the information given by the surgeon at the time of operation. The valve was examined before mitral commissurotomy was performed and repeated thereafter. This classification, although very simple, has proved to be useful and is sufficient for the practical purpose of this study.

The pathologic changes of the mitral valve have been summarized in the following three main groups.

Mitral Stenosis of Elastic Type.—At the time of the digital examination the valve leaflets appear elastic and yielding and show large displacements in relation to the phases of the cardiac cycle. Sclerotic changes are merely palpable at the valve's limbs; calcification is absent or very small and does not impair the mobility of the leaflets. Papillary muscles and chordae tendineae are usually undamaged.

Mitral Stenosis of Sclerotic Type.—The valve leaflets are rigid, thickened, and poorly yield. Small grainlike calcifications can be present on their surface.

The findings of subvalvular structures are quite variable. Pathologic changes can be completely absent or very mild, or fusion and shortening of papillary muscles and chordae tendineae can be found.

Mitral Stenosis With Diffuse Calcifications.—In this instance the pathologic changes are the most serious. The leaflets are severely damaged; diffuse sclerosis and large calcifications are present. Their normal shape has been lost because of irregularities and nodules which are felt under the surgeon's finger as a solid stonelike surface.

Chordae tendineae and papillary muscles are usually sclerotic, thickened, shortened, and fused together.

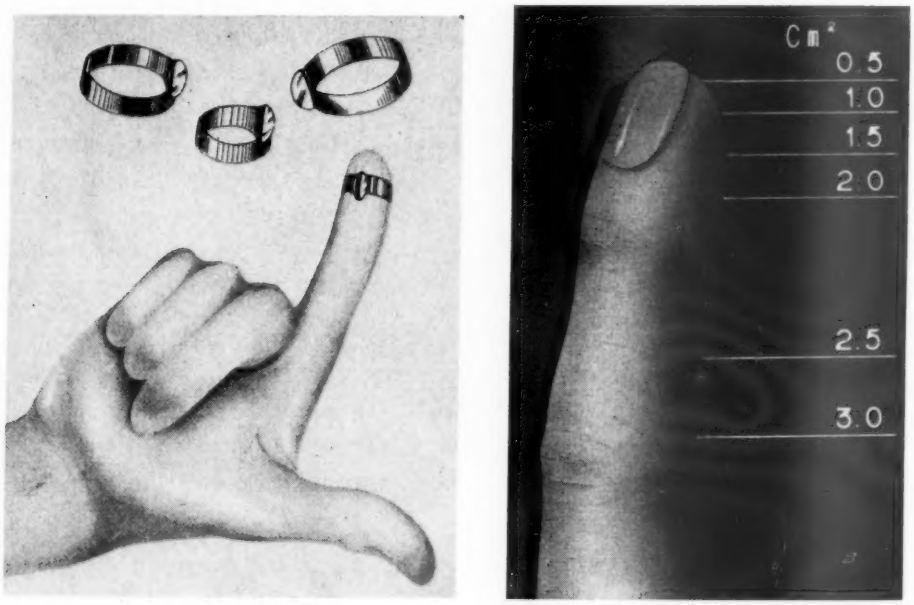
Calcification can be present in different amounts in all the afore-mentioned types of valvular changes. Three main forms may be found (as previously described by Bailey): (1) isolated pinpoint-like granules disseminated on the surface of the leaflets, (2) oblong plaques or nodules engraved in the thickness of the valve, and (3) diffuse infiltrations of the whole valvular structure.

If massive calcification is present, the mitral valve becomes a rigid ring whose internal surface is extremely irregular.

Calcium depositions are sometimes also found in the interior of the atrium and also in parietal thrombi or the auricle.

SURGICAL INSTRUMENT

Instrumental valvulotomy in almost all instances was performed by means of Dogliotti's finger-ring valvulotome. This instrument (as it is shown in Fig. 1) has a broad finger-ring shape and bears on its external surface a scimitar-like blade.



A. *B.*

Fig. 1.—*A*, The Dogliotti ring valvulotome. It is placed at the end of the finger with the scimitar-shaped blade oriented toward the commissure to be cut. *B*, The chalk outline of the finger of the operator. From how far it goes into the mitral ostium, we can measure the area in square centimeters.

The ring is put on the index finger of the surgeon so that the cutting edge of the blade is on the ventral side of the finger.

This instrument has proved to have many advantages: because of its small size it is very easily handled; the feeling of the surgeon's index finger is not hindered by wearing it; complete mobility of the finger inside the heart is allowed; and a perfect hemostasis from the auricle during commissurotomy can be maintained.

For these reasons we have used this instrument for most of the instrumental valvulotomies performed in our department; only in a few occasions a thimble has been used.

RESULTS OF ANALYSIS OF 2,000 CASES

Age and Sex.—Two thousand cases examined in this report include 674 men and 1,326 women (Table I). The male/female ratio was one to two.

The age range of our patients was between 10 and 56 years. However, 85 per cent of them were in the range of 20 to 45 (558 men and 1,153 women were included in these limits).

TABLE I. AGE AND SEX

SEX	AGE (YEARS)									
	10-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60
Male patients (674)	15	37	72	106	147	136	102	38	18	3
Female patients (1,326)	27	80	198	349	246	203	169	42	12	0

The male group had a mean age slightly higher than the female group, since most of the male population was from 31 to 40 years old while in the female group the most frequent age was between 21 and 30.

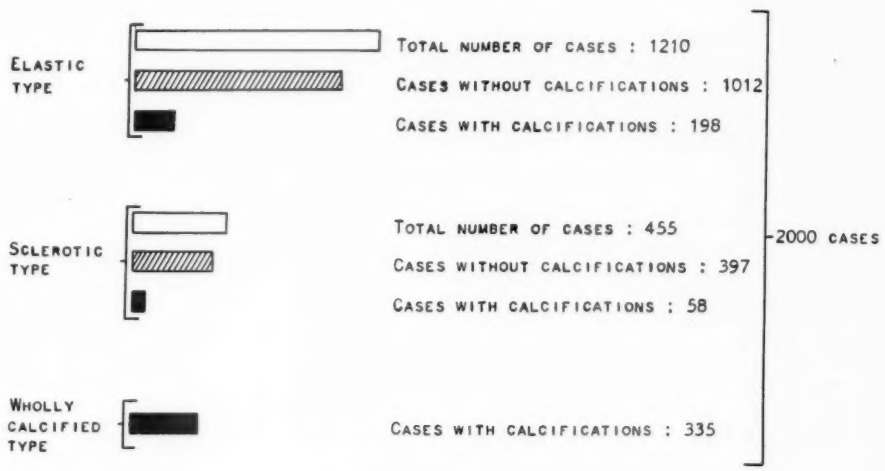

ELASTIC TYPE
TOTAL NUMBER OF CASES : 1210
CASES WITHOUT CALCIFICATIONS : 1012
CASES WITH CALCIFICATIONS : 198
SCLEROTIC TYPE
TOTAL NUMBER OF CASES : 455
CASES WITHOUT CALCIFICATIONS : 397
CASES WITH CALCIFICATIONS : 58
WHOLLY CALCIFIED TYPE
CASES WITH CALCIFICATIONS : 335
2000 CASES

Fig. 2.—Anatomic condition of the valves.

Valvular Types of Mitral Stenosis.—According to our classification the most common type of valvular pathology found in the present series of cases was the elastic one. From 2,000 cases, 1,210 (60.5 per cent) belonged to this group (Fig. 2). In 198 of these, small calcified nodules and disseminated calcareous plaques were present on the leaflet surface; however, their size was not such as to hamper the mobility of the valve.

The sclerotic type was found in 455 cases (22.7 per cent). Calcium deposits were felt in 58 cases, but in no instance were they of such an extent to compromise valvular function.

In 335 subjects (16.7 per cent) the surgeon found extensive calcific infiltrations of the valvular structures so that normal function was seriously handicapped.

Technical Approach Followed in Relation to the Valvular Conditions (Fig. 3).—The 1,210 valves of the elastic type have been operated upon as

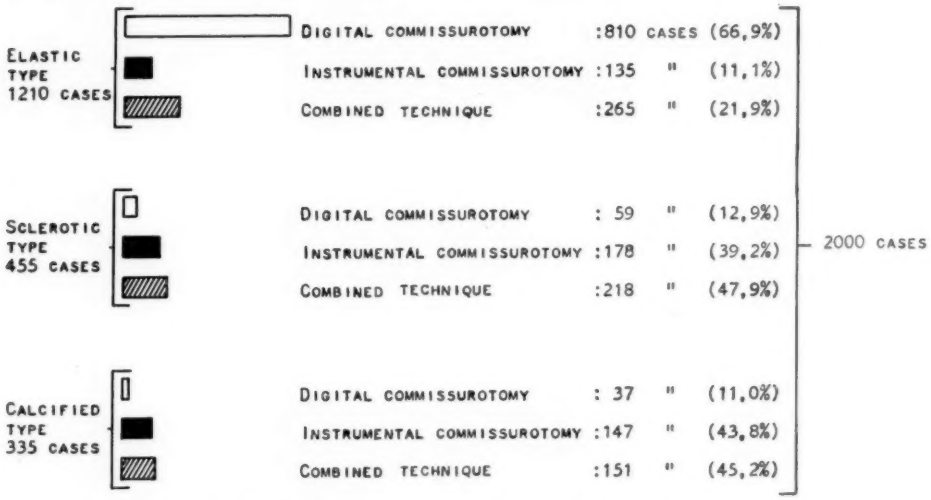

ELASTIC TYPE 1210 CASES
DIGITAL COMMISSUROTOMY :810 CASES (66,9%)
INSTRUMENTAL COMMISSUROTOMY :135 " (11,1%)
COMBINED TECHNIQUE :265 " (21,9%)
SCLEROTIC TYPE 455 CASES
DIGITAL COMMISSUROTOMY : 59 " (12,9%)
INSTRUMENTAL COMMISSUROTOMY :178 " (39,2%)
COMBINED TECHNIQUE :218 " (47,9%)
CALCIFIED TYPE 335 CASES
DIGITAL COMMISSUROTOMY : 37 " (11,0%)
INSTRUMENTAL COMMISSUROTOMY :147 " (43,8%)
COMBINED TECHNIQUE :151 " (45,2%)
2000 CASES

Fig. 3.—Surgical technique in relation to the valvular condition.

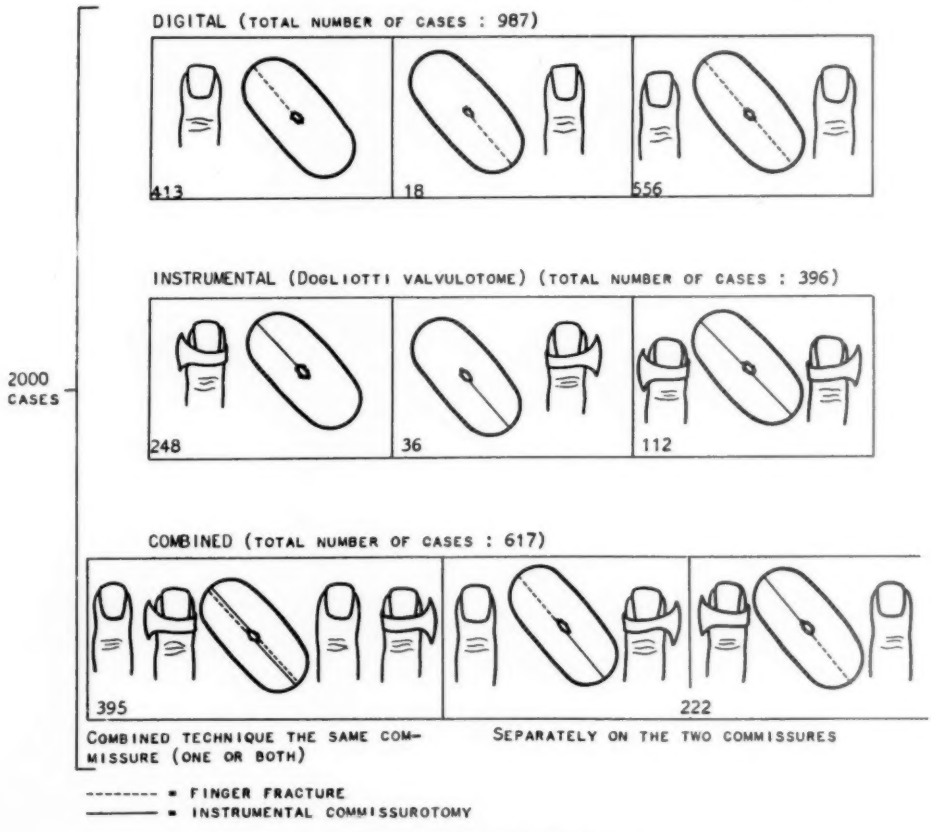
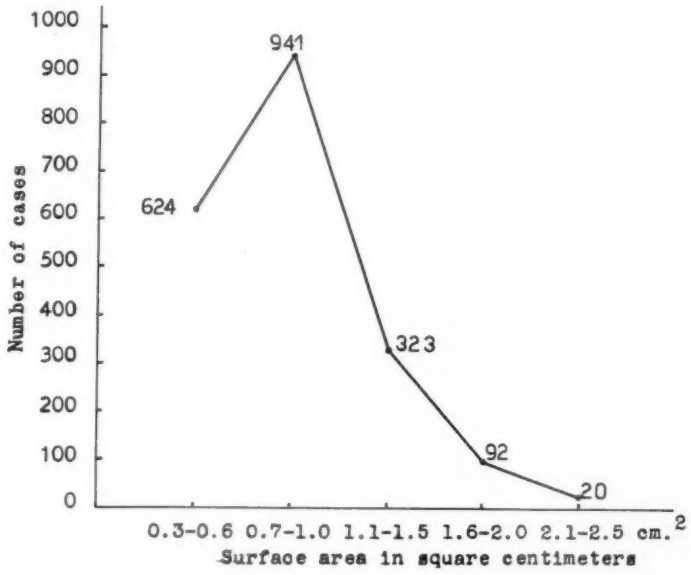


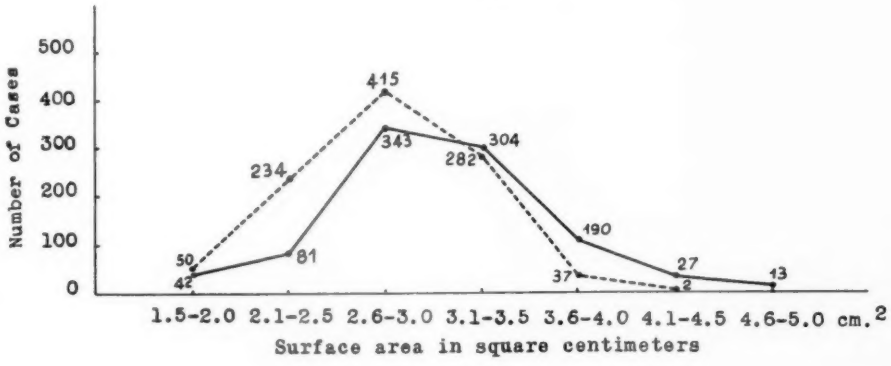
Fig. 4.—Surgical technique.

follows: 810 (66.9 per cent) by digital splitting, 135 (11.1 per cent) by instrumental commissurotomy only, and 265 (21.9 per cent) by both techniques.

Of 455 sclerotic-type valves, 59 (12.9 per cent) have been operated upon by digital splitting, 178 (39.2 per cent) by instrumental commissurotomy, and 218 (47.9 per cent) by combined technique. In the group with calcific-type valves (335 cases), satisfactory results were obtained by simple finger fracture in only 37 instances (11.0 per cent); 147 (43.8 per cent) were operated upon by instrumental valvulotomy, and 151 cases (45.2 per cent) by the combined technique.



A.



B.

Fig. 5.—*A*, Valvular area before intervention. *B*, Valvular area after intervention. - - - - - = First 1,000 cases. ——— = Next 1,000 cases.

From these data it follows that in most of the elastic-type valves a good technical result was achieved by simple digital splitting, while, in the sclerotic and calcific type, instrumental valvulotomy performed alone or with digital splitting was usually required.

Anatomic Results in Relation to Technical Approach (Fig. 4).—Of 2,000 cases, 987 were operated upon by digital splitting only (99.3 per cent). In

556 both commissures yielded; in 413 only the anterior one yielded and in 18 only the posterior one.

We have used instrumental commissurotomy only in 396 cases. In 112 patients both commissures were incised, in 248 only the anterior, and in 36 only the posterior one.

A combined technique was applied in the remaining 617 cases. In 395 of them, both techniques (finger fracture and instrumental valvulotomy) were applied on both commissures, while in 222 one commissure was split by digital fracture only and the other by instrumental valvulotomy only.

In general, the anterior commissure was the most frequently divided, whether it be by finger fracture or by instrumental incision.

Ostium Surface (Fig. 5).—The size of the ostium was determined by measuring the diameter of the exploring finger at the level at which it became engaged in the mitral orifice.

Thirty-one per cent of the patients had a very tight mitral stenosis (mitral orifice of 0.6 cm.^{2} or less), and 47 per cent had a tight mitral stenosis (orifice diameters between 0.6 and 1 cm.^{2}). In 16 per cent the diameter of the orifice was between 1 and 1.5 cm.^{2} and only in the remaining 6 per cent was the diameter larger than 1.5 cm.^{2}

We will report separately the results obtained in the first 1,000 cases, since in the last 1,000 patients a larger degree of dilatation was generally obtained.

In the first 1,000 cases the final mitral valve diameter was: in 41.5 per cent between 2.6 and 3 cm.^{2}, in 26.2 per cent between 3.1 and 3.5 cm.^{2}, and in 3.7 per cent between 3.6 and 4 cm.^{2}. In the remaining 28.4 per cent the mitral orifice after commissurotomy remained less than 2.5 cm.^{2} in diameter.

In the next 1,000 patients the following results were obtained. In 4 per cent the final surface of the ostium was larger than 4 cm.^{2}. In 19 per cent it was between 3.6 and 4 cm.^{2}, in 30 per cent between 3.1 and 3.6 cm.^{2}, in 34 per cent between 2.6 and 3.1 cm.^{2}, in 8 per cent between 2.6 and 2 cm.^{2}, and in 5 per cent between 1.5 and 2 cm.^{2}.

From these data it is clear that in the second thousand cases greater enlargements of the ostium were obtained. This result has been explained by the fact that we had more knowledge of the pathologic anatomy of the mitral valve and more experience in the techniques of commissurotomy. Moreover, we knew then that the best functional results are obtained in those subjects in which the greatest enlargements are obtained. For this reason now we attempt to enlarge the ostium to a surface size as near normal as possible.

It is of great interest in this regard that despite the greater enlargement of the orifice, no increase in surgically provoked insufficiency was observed.

It was also noticed that (1) the initial size of the ostium has no relation to how much enlargement of the ostium is obtainable and (2) the 3 methods of commissurotomy give identical results if applied to the same type of case using criteria that we will point out later.

Occurrence of Mitral Insufficiency.—Minimal or moderate mitral insufficiency was recognized at the time of digital exploration of the mitral valve in 276 cases. As shown in Table II, it remained unchanged in most of the cases after commissurotomy was performed. In 29 it diminished or disappeared. In 53 subjects the degree of insufficiency increased. In 36 patients an insufficiency of variable degree was created.

TABLE II. SURGICAL TECHNIQUE IN RELATION TO MITRAL INSUFFICIENCY

	REGURGITATION			
SURGICAL TECHNIQUE	APPEARED	INCREASED	UNCHANGED	DECREASED OR DISAPPEARED
Digital	17	18	112	4
Instrumental	9	16	89	13
Combined	10	19	103	12

Lacerations.—This complication occurred in 58 cases of 2,000, but in only 3 did it include the whole atrial wall. In the remaining 54, the laceration was limited to the point of insertion of the left auricular appendage into the left auricle.

All lacerations occurred during digital splitting maneuvers, except two which happened during instrumental valvulotomy. In one instance tearing of a valve leaflet occurred.

TABLE III. SURGICAL TECHNIQUE IN OCCURRENCE OF LACERATIONS

	LACERATIONS		
SURGICAL TECHNIQUE	BASE OF AURICULAR APPENDAGE	ATRIAL WALL	VALVULAR LEAFLET
Digital	49	3	1
Instrumental	2	0	
Combined	3	0	

Over-all Operative Mortality.—The operative mortality (intervention and 30 days postoperatively) was higher in the first hundreds of cases and lower in the following ones, although many patients of the latter groups had been operated upon in worse conditions, were older, and suffered from combined valvular lesions.

Of 2,000 patients we had 61 deaths (3.05 per cent). The total mortality was as follows: 9 in the first 100 patients (9 per cent), 3 in the second 100 (3 per cent), 2 in the third 100 (2 per cent), and 3 cases in the fourth and fifth 100 (3 per cent). Death occurred in 20 (4 per cent) of the first 500 patients, in 19 (3.8 per cent) of the second 500, in 15 (3 per cent) of the third 500, and in 7 (1.4 per cent) of the fourth 500.

Mortality Rate in Various Groups.—Of 1,210 patients with elastic valves, death occurred in 30 (2.48 per cent). Of 455 patients with sclerotic valves, death occurred in 12 (2.87 per cent). Of 335 patients with calcified valves, death occurred in 19 (5.67 per cent). The over-all mortality resulted lowest in the group of patients with elastic valves, slightly higher in the patients with sclerotic valves, and most elevated in those with calcified valves.

DISCUSSION

From the analysis of the data presented in the first part of this paper we can draw the following conclusions:

1. The separation of commissures by digital pressure only is indicated whenever stenosis is chiefly due to fusion of the commissures (first type of stenosis according to our classification). The leaflets are still elastic and do not show sclerosis or calcifications. In these cases a complete separation of the valve leaflets can be obtained by simply pressing on the commissures so that an optimal dilatation of the orifice with good functional improvement can be achieved.

2. Therefore a good surgical result may be obtained by finger fracture alone in the elastic type of mitral stenosis with no sclerosis or calcification of the commissures.

However, it sometimes happens that this maneuver fails in the presence of a bridge of fibrous tissue across one or both of the elastic leaflets. In this case the finger will feel an elastic resistance and a yielding of the valvular apparatus, but no splitting of the commissures will occur.

Digital splitting, on the other hand, can be completely satisfactory in the presence of sclerotic and even calcified valvular structures if sclerosis or calcifications are limited to leaflet surface without involvement of the commissures and if only some relatively soft tissue keeps the cusps adherent.

3. If by digital splitting the surface of the orifice can be enlarged to 3 to 3.5 cm.^{2}, the surgical results can be considered satisfactory. It is desirable, however, to cut the commissure up to the A-V ring and for the same reason, if possible, the chordae tendineae near the commissure should be isolated.

On the other hand an enlargement of the mitral ring to 2.5 to 3 cm.^{2} can be considered highly satisfactory if because of local conditions further trials would be dangerous. This will be the case if thrombi are present in the left atrium or if verrucosities or particles of calcium have been felt on the valve cusps or near the commissures, which could be easily dislodged by repeated maneuvers.

4. When a sufficient separation of the commissures has not been achieved after forcible finger pressure, to further continue the manipulations can prove to be very dangerous because of the following possibilities: (a) easier laceration of the auricular appendage at its base, (b) increased possibility of mobilization of atrial thrombi, (c) excessively maintained occlusion of the A-V orifice, (d) occurrence of cardiac arrhythmias due to excessive pulling on valvular leaflets, and (e) improper enlargement of the orifice by laceration of the leaflets outside the commissure.

5. Digital pressure first must be applied on the anterior commissure and next on the posterior one. Although in most cases the splitting maneuvers are mainly performed on the anterior commissure, pressure should be directed toward that commissure which at exploration seems the easier to split. As a matter of fact, in many instances one commissure is sclerotic or deeply calcified, while the other one is still elastic and yields easily to the finger. In these cases the complete separation of the softer commissure can produce a dilatation up to 3 to 3.5 cm.^{2} which has to be considered sufficient.

6. Indications for instrumental commissurotomy arise in those cases in which digital pressure did not succeed or the obtained enlargement was considered to be inadequate with respect to the age and body surface of the patient.

7. Instrumental valvulotomy is suggested in the presence of: (a) sclerotic commissures resistant to digital pressure and (b) extensive calcifications of the commissures. In this last group common valvulotomes are sometimes insufficient to cut the very resistant structures found. Therefore, valvulotomes maneuvered externally will be necessary, like the Du Bost type.

8. It is advisable at first to direct instrumental commissurotomy on the commissure which is farther from the A-V ring. In this way the best enlargement of the ostium will be obtained. However, it would be better if both commissures were split up to the fibrous ring so that better mobility of the leaflets could be achieved. If one of the commissures is severely calcified while the other one is of the elastic or fibrous type, it is on this last one that digital or instrumental maneuvers will have to be applied.

9. For restoration of maximal cusp mobility instrumental commissurotomy should attempt to extend the incision of the commissure up to the optimal limit which is represented by the fibrous ring. In some cases, however, the surgeon meets anatomic situations in which all attempts will succeed poorly.

These conditions are chiefly represented by retracted valvular leaflets which have completely lost their original shape by fusion of chordae tendineae and by papillary muscles which form a musculofibrous canal. In these cases digital separation as well as instrumental valvulotomy are likely to be unsuccessful.

10. Instrumental valvulotomy does not represent a more serious surgical risk than digital splitting. This statement will hold true particularly if the Dogliotti valvulotome is used because of its practical advantages. Some difficulties will arise if there is a narrowing of the base of the left atrial appendage.

As far as maneuvers on the leaflets are concerned, instrumental valvulotomy avoids the traumas produced by excessive pressure and by stretching of valvular structures, which are sometimes necessary if a digital splitting has to be performed.

As described by some authors, an arterial branch of the left coronary artery may be cut when an incision of the anterolateral commissure is carried too deeply beyond the A-V ring. This accident never occurred in this series, and we think it can be easily avoided.

It is our opinion that instrumental valvulotomy, although not always necessary, is a safe procedure and must be used any time that any of the aforementioned complications are present.

11. Among the many instruments for commissurotomy described in the literature, the Dogliotti valvulotome has proved in our experience to be the simplest and the easiest to handle. Moreover, it gives optimal results in practically all instances unless massive calcific depositions of the commissures exist.

12. Instrumental valvulotomy is—as we have already stated—a technique which has to be used to complete the results of the finger fracture technique.

13. The occurrence of complications, such as atrial lacerations, mobilization of thrombi, occurrence of valvular regurgitation, atrial hemorrhage, and cardiac

arrhythmias, is definitely higher in those patients in whom digital pressure was done, compared with those in whom instrumental valvulotomy was performed. As a matter of fact, laceration of auricular appendages and of atrial walls occurs with greater ease during digital maneuvers. As blunt pressure is applied on the stenotic valve, the sudden release of this resistance on separation of the commissures will cause the finger of the operator to be forcibly pushed against the left auricle; in some instances tearing of the valve can occur.

14. The results obtained with instrumental commissurotomy, either as the sole technique or associated with digital pressure, are definitely better than those obtained with the single finger fracture technique because of the better functional mobility obtained and also because of the lower incidence of complications.

15. The general mortality of 2,000 patients was 61 (3.05 per cent). It was lower in patients with elastic valves, slightly higher in those who presented sclerotic valves, and remarkably stronger in the patients having wholly calcified valves. We have not observed peculiar differences of mortality according to the techniques employed. We have already pointed out that mortality seemed to be more related to the anatomic condition of the stenotic valve.

SUMMARY

We have presented 2,000 cases of valvulotomy for mitral stenosis and discussed the techniques used with respect to anatomicopathologic conditions of the valve (instrumental or digital). Anatomic and functional results are discussed also.

The technical considerations to be followed in deciding which method to use are described on the basis of personal experience.

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SURGICAL CORRECTION OF CHRONIC MITRAL INSUFFICIENCY IN DOGS

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MITRAL insufficiency persists as a serious sequela of rheumatic heart disease. Although patients with mitral stenosis may be greatly benefited by operation, the surgical correction of mitral insufficiency has been less successful. There has been little agreement among surgeons as to the most effective method, and the large variety of approaches to the problem attests to the inadequacy of any one procedure. Most techniques have been based upon the principle of supplying substitutes for the lack of valve substance. More recently, attempts have been made to reduce the circumference of the mitral ring in such a way that the shortened valve leaflets can more adequately occlude the mitral orifice.

Previous investigators have tested corrective techniques only in animals with acutely created insufficiency. The present study was undertaken for the purpose of evaluating in dogs methods of correction of mitral insufficiency which was chronic in nature. The anatomic and pathologic defects produced in the experimental animals approximated those seen in human beings with this disease.

MATERIALS AND METHODS

Corrective procedures were performed in 20 adult mongrel dogs with severe chronic mitral insufficiency of 2 to 6 months' duration. A controlled degree of insufficiency had been produced in these dogs by a previously reported method[5, 6] of engaging chordae tendineae attached to the posterior leaflet with a hook and then suturing them down to the left ventricular wall, as illustrated in Fig. 1.

The operative techniques used to correct the insufficiency were (1) a distorting or reefing suture placed in the posterior portion of the mitral ring (Fig. 2, *right*) and (2) a circumferential suture of the mitral ring (Fig. 2, *left*). In order to perfect the techniques before proceeding with the present study, both of these procedures were performed on a number of fresh dog hearts obtained at necropsy and on living hearts at thoracotomy in normal dogs and in dogs with acute mitral insufficiency.

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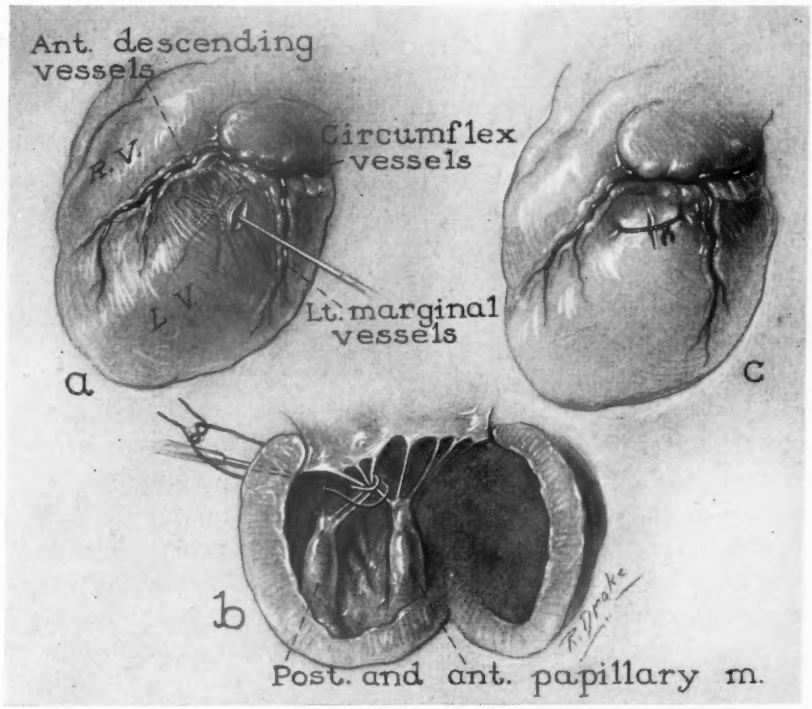

Fig. 1.—The method of producing chronic mitral insufficiency. *a*, The site of the incision. The hook engaging the chordae is within the left ventricle. *b*, The hook holding chordae of the posterolateral cusp against the endocardium during placement of the encircling suture. *c*, The position of the finished suture. The polyvinyl sponge over which the suture is tied is not shown in the drawing. (Reproduced with permission from Kuykendall, S. J., Ellis, F. H., Jr., Grindlay, J. H. and Wood, E. H.: The Surgical Production of Chronic Progressive Mitral Insufficiency in Dogs, S. Forum 7: 237, 1957.)

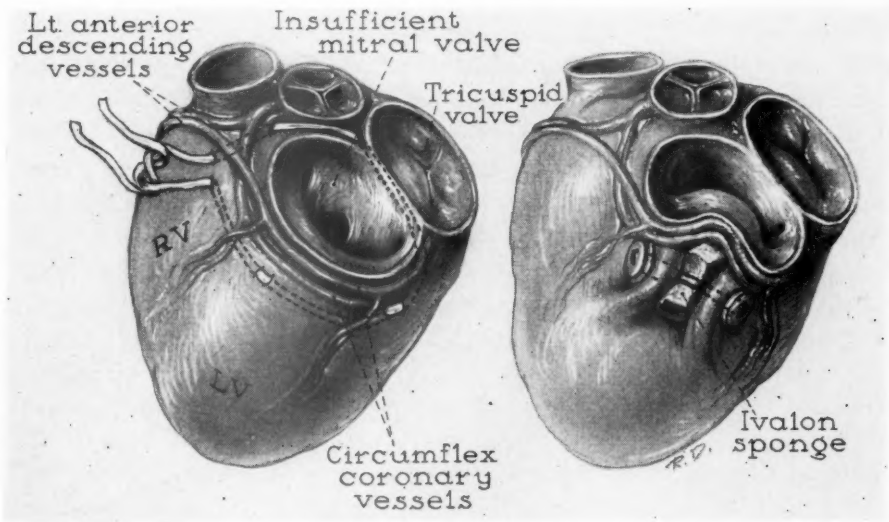

Fig. 2.—The two methods used for the correction of mitral insufficiency. *Left*, the position of the finished circumferential suture prior to tying the suture and constricting the mitral ring. *Right*, the final position of the distorting suture with the resultant inward displacement of the posterior portion of the mitral annulus.

Technique of Distorting Suture of the Mitral Annulus.—The dogs were anesthetized with ether and oxygen. Respiration was maintained by endotracheal oxygenation under intermittent positive pressure from a mechanical respirator. The thorax was entered by a left anterolateral incision through the fifth intercostal space. The pericardium was opened parallel and anterior to the left phrenic nerve, and the margins were retracted outward with weighted traction sutures. A hemostatic purse-string suture was placed about the base of the left atrial appendage. The tip of the appendage was amputated and the surgeon's left index finger was inserted into the atrium. A doubled, heavy-braided silk suture was placed through the fibrous annulus along the attachment of the mural cusp with a long needle and was tied over plastic buttons covered with compressed polyvinyl sponge (Ivalon), which were placed just anterior to the posterior descending coronary vessels and just posterior to the anterior descending coronary vessels as shown in Fig. 2, *right*. (With the passage of time the Ivalon was invaded with noninflammatory fibrous tissue and was incorporated into the tissue of the exterior of the heart, thus preventing the plastic buttons from eroding into the myocardium.) Tying the suture down resulted in an inward bulging of the posterior portion of the annulus, thereby narrowing the mitral ring. An intra-atrial finger at the mitral orifice determined the tension necessary to obliterate regurgitation completely without producing stenosis. (From the technical standpoint, however, a guiding finger within the heart is not actually necessary for placement of the suture.) The finger was withdrawn from the heart as a clamp was applied across the base of the atrial appendage, and the defect in the appendage was closed. The pericardium was loosely approximated, and the chest was closed in layers.

Technique of Circumferential Suture of the Mitral Annulus.—The animals were anesthetized, the left heart was exposed, and a finger was inserted into the atrium as described. The circumferential suture was placed in a fashion similar to that described by Davila and Glover and associates,[2, 3] using the suture carrier they designed. The needle entered the myocardium at the posterior aspect of the annulus just to the left of the posterior descending coronary vessels and immediately beneath the coronary sinus. It then was passed within the substance of the annulus posteriorly and medially either through the base of the interatrial septum (emerging in the transverse sinus at the junction of the anterior atrial walls with the septum) or through the right atrial cavity (entering beneath the opening of the coronary sinus and emerging anteriorly at the junction of the right atrium with the septum). Care was taken not to enter the left atrium, since when this occurred and the completed suture was tied down, the suture would cut through the atrial wall. Having moved so far, the needle was threaded in the transverse sinus with braided cotton umbilical tape and drawn back through to the starting point. Then the posterior tail of the suture was threaded on a large, curved, Mayo-type needle and passed within the tissue of the annulus and beneath the branches of the circumflex vessels to emerge just to the left of the anterior descending coronary vessels. A tunnel was then made with a small, curved hemostat deep to the circumflex

coronary vessels, and the anterior tail of the suture was drawn through beneath these vessels to meet the posterior tail. The ends of the suture were snugged down by the assistant until the regurgitant jet no longer could be felt by the intra-atrial finger, and the suture was tied with a triple square knot.

When the anterior portion of the suture emerged from the right atrium, troublesome bleeding frequently occurred at this point, necessitating repair of the small tear. However, when the anterior portion of the suture emerged from the base of the interatrial septum, bleeding was not a problem. A pericardial bolster over the right atrial portion of the suture, as advocated by Davila and associates,[2] was not used, since cutting through of the right atrial portion of the suture was not found to be a problem in this series. When the circumferential suture cut through in the dogs in the present series, it did so around its entire circumference, cutting its way inward with its path scarring in behind it. The suture did not enter the left atrium in any of the animals. There was never any apparent disturbance of coronary circulation.

After the circumferential suture was tied, the surgeon's finger was withdrawn from the heart as a clamp was applied across the base of the atrial appendage. The defect in the appendage was closed. The pericardium was partially approximated, and the chest wall was closed in layers.

Comparison of Techniques.—The distorting procedure has several technical advantages: (1) it is easier and quicker to perform, (2) minimal manipulation of the heart is necessary, (3) there is no danger of piercing or occluding the coronary sinus, and (4) there is no danger of damage to the circumflex coronary circulation.

RESULTS

Twelve dogs survived corrective operations. The mitral insufficiency had been corrected in 6 of the surviving dogs by the reefing suture technique and in the other 6 by the circumferential suture technique. In all dogs of both groups the immediate correction had been adequate as judged by the disappearance of the regurgitant jet in the left atrium at the time of operation.

Clinical Manifestations.—Immediately after operation all of the dogs were found to have normal heart sounds, rate, and rhythm. A definite change was noted in the behavior of the dogs within a few days. Whereas previously they had been dyspneic on exertion and easily fatigued, now they became playful, and moderate exercise no longer seemed to produce abnormal panting.

The dogs were observed for periods varying from 71 to 350 days. A recurrent systolic murmur developed in only one of the 6 dogs in which the regurgitation was corrected by the distorting suture technique (Table I). The murmur was first detected in the second postoperative month. In contrast, systolic murmurs developed postoperatively in 5 of the 6 dogs in which the regurgitation was corrected by the circumferential suture technique (Table II), and in 3 of these it was detected within one month after correction. These latter 3 dogs also exhibited recurrence of their exertional dyspnea. With respect to heart size, repeated thoracic roentgenograms revealed no significant change from the precorrection roentgenograms in any of the animals.

TABLE I. CORRECTION OF CHRONIC MITRAL INSUFFICIENCY BY DISTORTING SUTURE OF THE MITRAL ANNULUS

DOG	MURMUR		REOPERATION	
	IMMEDIATELY AFTER CORRECTION	SUBSEQUENTLY	RECURRENCE OF MITRAL INSUFFICIENCY	DAYS AFTER CORRECTION
1	0	0	0	71
2	0	0	0	291
3	0	0	0	193
4	0	0	0	331
5	0	Grade 2-3	Yes	350
6	0	0	0	196

TABLE II. CORRECTION OF CHRONIC MITRAL INSUFFICIENCY BY CIRCUMFERENTIAL SUTURE OF THE MITRAL ANNULUS

DOG	MURMUR		REOPERATION	
	IMMEDIATELY AFTER CORRECTION	SUBSEQUENTLY	RECURRENCE OF MITRAL INSUFFICIENCY	DAYS AFTER CORRECTION
7	0	Grade 2	Yes	73
8	0	Grade 2	Yes	342
9	0	Grade 3	Yes	133
10	0	0	0	196
11	0	Grade 4	Yes	297
12	0	Grade 3	Yes	184

Physiologic Changes.—Direct pressure recordings and dye-dilution curves were made before and after correction in some of the animals.* An example of pressure recordings is shown in Fig. 3. The change in the left atrial pressure recordings is especially noteworthy. An example of dye-dilution curves simultaneously recorded at the femoral artery and in the left atrium after left ventricular and left atrial injection is shown in Fig. 4. Normally, after dye is injected into the left ventricle, none should be detectable in the left atrium until after it has appeared in the femoral artery. In the presence of chronic mitral insufficiency, however, the recording made after left ventricular injection shows this sequence in reverse. The dye curve made after partial correction of the insufficiency shows a return toward normal of measurements from the left atrium after left ventricular injection.

Findings at Later Surgical Exploration.—The dog in which a systolic murmur developed after distorting suture correction of the mitral insufficiency was found to have a moderate degree of mitral regurgitation at surgical exploration one year after correction (Table I). The degree of recurrent regurgitation was somewhat less than that which originally existed. No regurgitation could be found at surgical exploration in the other 5 dogs 71 to 331 days after correction by the reefing suture method.

All 5 of the dogs whose mitral regurgitation was corrected by the circumferential suture technique and which had recurrent systolic murmurs were found at surgical exploration 73 to 342 days after correction to have a recurrence of regurgitation equal, or almost equal, in degree to that which originally existed (Table II). The one dog in which a systolic murmur did not

*All physiologic studies were performed with the professional assistance of Dr. E. H. Wood.

develop was found to have no evidence of recurrence of mitral regurgitation at exploration 196 days after correction of the regurgitation by the circumferential suture technique.

Surgical exploration was carried out under general anesthesia in all of the animals. The dogs were then killed for necropsy study by an intracardiac injection of an overdose of pentobarbital sodium.

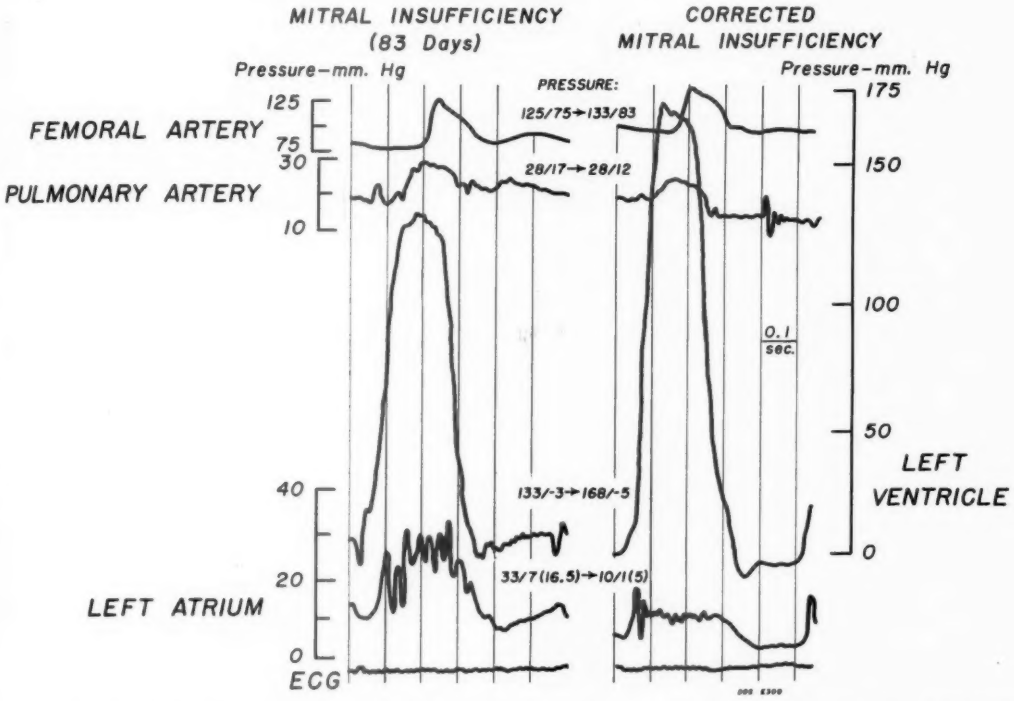

Fig. 3.—Direct pressure curves taken simultaneously during thoracotomy in a dog with chronic mitral insufficiency, before (*left*) and after (*right*) correction of the insufficiency. Note the change in the left atrial pressure from an elevated mean of 16.5 mm. Hg in the presence of chronic mitral insufficiency to a mean of 5.0 following correction.

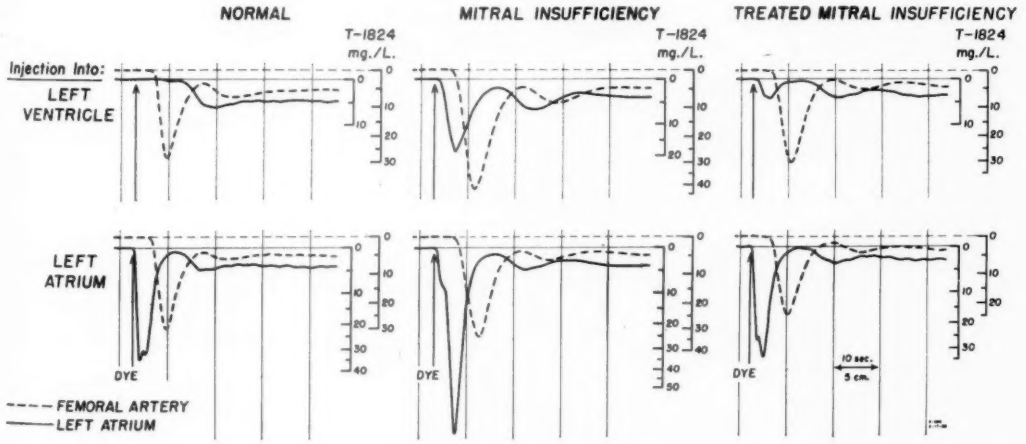

Fig. 4.—Simultaneous dye-dilution curves recorded at femoral artery and left atrium after left ventricular and left atrial injections during thoracotomy in a dog before creation of mitral insufficiency (*left*), after creation of mitral insufficiency (*center*), and after correction of mitral insufficiency (*right*). The dog weighed 18 Kg. and the dye dose was 5 mg. of T-1824. Note the indication of the appearance of dye in the left atrium before it appears in the femoral artery in the presence of mitral insufficiency (*center*) and the change back toward normal immediately after correction of the insufficiencies (*right*).

Pathologic Findings.—The 2 plastic buttons were found in closer proximity than originally placed in the one dog which had recurrence of regurgitation following the reefing suture correction. There was no change in the position of the buttons in the other 5 dogs.

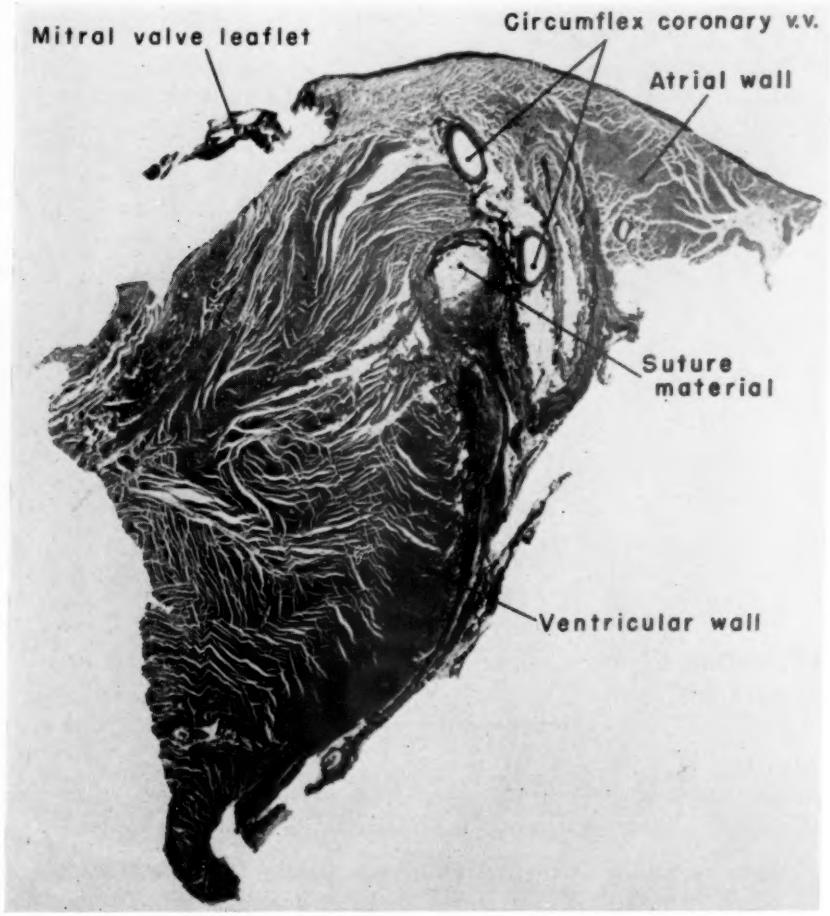

Fig. 5.—The site of the suture at necropsy in a dog which had recurrent mitral insufficiency after correction by the circumferential suture technique. The path of scar tissue behind the suture (right of ventricular wall as shown) indicates the manner in which it cut through the cardiac tissues toward the heart chamber and lost its corrective effect by becoming loosened (van Gieson's elastic-tissue stain; ×6).

In the 5 dogs with recurrent mitral regurgitation in which correction was accomplished by the circumferential suture technique, the suture had cut through the tissue of the mitral annulus centripetally around its entire circumference like a rope cutting through a block of ice (Fig. 5). The suture did not cut into the heart chamber. In 2 of the 5 this finding was apparent on gross examination of the hearts. In the sixth dog, the circumferential suture held its initial position, and adequate correction of the previously existing regurgitation was maintained.

COMMENT

From this small series of animals, it appears that the effectiveness of the corrective procedures directed toward narrowing of the orifice of the mitral ring

is significantly altered by the use of dogs with chronic mitral insufficiency and dilated mitral rings, as compared with dogs with acute mitral insufficiency and normal mitral rings. Earlier experiments in our laboratory,[4] as well as those of Davila and associates[2] and Borrie,[1] have shown that circumferential suture techniques adequately correct insufficiency in a high percentage of animals with acute mitral insufficiency and normal mitral rings. In such animals, the suture needs to be snugged down very little to correct the regurgitation. A condition more closely simulating mitral insufficiency in human beings is reproduced in dogs with chronic mitral insufficiency and dilated mitral rings. In these animals more tension on the suture is necessary to correct the regurgitation, with the result that the suture tends to cut through the tissues of the heart toward the heart chamber. In time its effectiveness as a circumferential constricting suture may be partially or completely lost thereby.

Although the results achieved with the distorting suture procedure appeared promising in this small series of dogs, we are hesitant to recommend its use clinically. It appears that corrective procedures directed toward narrowing of the mitral ring by a closed approach are of limited value in the treatment of mitral insufficiency. Perhaps the solution to the problem of the correction of mitral insufficiency lies in open, intracardiac repair of the defect under direct vision or insertion of a prosthesis to replace the defective valvular-tendon mechanism.

SUMMARY

Chronic mitral insufficiency was produced in dogs by a method previously described. The pathologic and physiologic defects in these animals closely simulated the disease as seen in human beings.

Two techniques for the correction of mitral insufficiency, directed toward reducing the circumference of the mitral ring, were tested in these animals. Initially the mitral insufficiency was corrected adequately by both techniques, as was borne out by the disappearance of the intra-atrial jet on palpation and the changes in the intracardiac pressures and dye-dilution curves.

Five of the 6 dogs in which correction was carried out by the circumferential suture technique exhibited recurrent murmurs and recurrence of the regurgitation at later surgical exploration. Only one of the 6 dogs in which correction was carried out by the distorting suture technique exhibited a recurrence of the regurgitation at later exploration.

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THE EFFECT OF HYPERCHOLESTEROLEMIA UPON AORTIC HOMOGRAFTS AND TEFLON-NYLON PROSTHESES IN THE RABBIT

Absence of Arteriosclerosis in Prostheses

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ARTERIOSCLEROSIS produced in the rabbit by high cholesterol feeding, first demonstrated by Anitschow,[2] and a similar arteriosclerosis produced in the dog by a combination of high cholesterol intake and hypothyroidism (Steiner and Kendall[10]) provide suitable testing grounds for the arteriosclerotic potential of arterial replacements.

Fisher,[7] by feeding a high cholesterol diet to the rabbit, showed that the experimental arteriosclerosis so induced developed to a more severe degree in homografts than in the host aorta.

We realize that one cannot transfer interpretations derived from studies with experimental rabbit cholesterol atherosclerosis directly to the human vascular systems, but we still agree with Duff[6] that this type of cholesterol sclerosis is in many respects similar to human arteriosclerosis and that the basic mechanism is probably the same. We believe that arteriosclerosis induced in rabbits by feeding a diet high in cholesterol is a particularly useful tool to test the behavior of materials used as arterial replacements since microscopic arteriosclerotic lesions are found as early as 26 days and gross lesions within 6 weeks.

In the experiments to be reported we assessed the arteriosclerotic potential of 2 types of vessel replacements: (1) lyophilized homografts and (2) Teflon-nylon prostheses.

MATERIAL AND METHODS

Adult albino rabbits weighing 4 to 5.5 Kg. and equally divided as to sex were utilized in this study. The animals were anesthetized with sodium Pentothal (10 mg. per kilogram) and the abdominal aorta was approached through a transabdominal incision.

It was established in preliminary experiments that 12 minutes was the maximum time that the lower aorta could be occluded without spinal injury. Clamping in excess of this time limit resulted in irreversible hindquarter paralysis and rapid deterioration of the animal leading to death. This is due

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to the comparatively primitive stage of evolution of the vascular supply to the spinal cord in the rabbit as pointed out by Stenonis in 1669—quoted by Adams and associates.[1]

In order to minimize the length of time during which the blood flow was interrupted, we used a modification of the technique originally suggested by Carrel[3] in 1910. Short sections of polyethylene tubing, 2.5 cm. in length, measuring 3 mm. in external diameter with a 2.0 mm. internal lumen, were grooved circularly with thermocautery 4 to 5 mm. from each end. These grooves formed a grip for the retaining ligature sufficient to hold the arterial end in place. The inside surface of these tubes was coated with heparin and the proposed replacement threaded over the tubing. After the abdominal aorta had been exposed and freed for a distance of 2 to 3 cm., bulldog clamps were placed at the proximal and distal end of the segment and the aorta was divided and allowed to retract. No segment of the aorta was removed. The ends of the tube were than inserted into the proximal and distal aortic lumen and secured by ties placed over the grooves, leaving a 2 to 3 mm. cuff between the ties at each end. The bulldog clamps were then removed and the circulation restored through the tube. This procedure required from 4 to 6 minutes. The entire proximal anastomosis and the posterior part of the distal anastomosis were then completed using 5-0 arterial silk as a continuous suture, interrupted at 4 points to avoid constriction of the lumen. The bulldog clamps were then reapplied, the intubation tube removed, and the distal anastomosis completed. This procedure took approximately 8 minutes. The circulation was then restored by removing both bulldog clamps. Moderate leakage occurred at the suture line and through the prosthesis (when these were used), but it was easily controlled by light pressure for 4 to 5 minutes.

In one series, lyophilized, freeze-dried homografts were implanted. These had been taken under sterile conditions 4 to 8 days earlier from sacrificed animals. They were prepared in a freeze-drying setup and stored under vacuum as described by Pate and Sawyer.[8] Short, straight segments of grafts about 1.5 cm. in length were used, and these grafts matched, as closely as possible, the size of the recipient aorta.

The second type of replacement consisted of a seamless woven tube, of nylon and Teflon 3.25 mm. in diameter which had been produced for us by J. Sidebotham.* This tube was woven with nylon thread as warp and Teflon as filling in a very tight taffeta weave. This tube was cut into 1.5 cm. segments and the cut edges were sealed by heat which melted down the nylon warp and fused the end very well. They were sterilized by autoclaving.

The animals received a slow intravenous drip of 5 per cent dextrose in water with 10 mg. of heparin per 100 ml. during the operation. Usually 30 to 50 ml. of this solution was given.

Postoperatively, the animals were fed 1 Gm. of cholesterol in 100 Gm. of Purina rabbit pellets. The cholesterol was administered as purified cholesterol powder which was dissolved in ether. This ether solution was then poured over the pellets and the ether allowed to evaporate, leaving a thin coating of cholesterol on the pellets.

*John Sidebotham, Inc., 4317 Griscom Street, Philadelphia 24, Pa.

The animals were sacrificed with Somlethal intravenously 45 to 96 days after operation and the aorta was removed. Cholesterol determinations were carried out on blood obtained by venipuncture previous to sacrifice.

Two grafted animals were fed regular pellet rations without cholesterol supplement to serve as controls. Nylon-Teflon prosthesis was placed in one and lyophilized homograft in the other.

RESULTS

Of the 36 animals operated upon, 22 survived surgery and 14 died from operative shock or other causes. Nylon-Teflon prostheses were implanted in 12 and homografts in 10.

Nylon-Teflon.—In the group of animals receiving nylon-Teflon prostheses, no arteriosclerotic changes were observed in the graft, although marked arteriosclerosis appeared in the immediately adjacent host aorta. The results are listed in Table I.

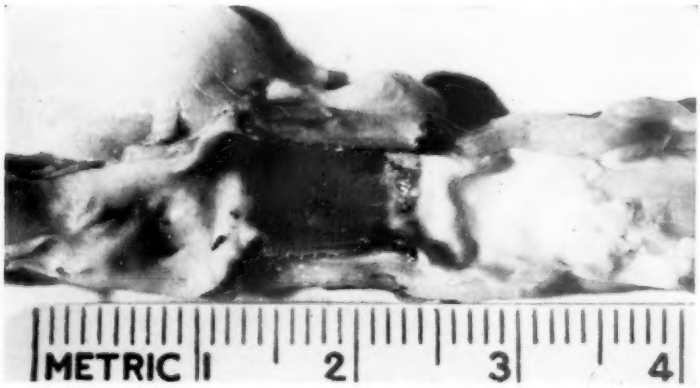

Fig. 1.—Teflon-nylon prosthesis implanted for 96 days in cholesterol-fed animal.

TABLE I. TEFLON-NYLON PROSTHESIS

ANIMAL NUMBER	POSTOPERATIVE DAYS	DIETARY SUPPLEMENT	ARTERIOSCLEROTIC CHANGES	
			HOST AORTA	REPLACEMENT
105	94	Cholesterol	Marked	None
107	97	Cholesterol	Marked	None
108	93	Cholesterol	Marked	None
109	96	Cholesterol	Marked	None
112	94	Cholesterol	Marked	None
113	93	Cholesterol	Marked	None
115	47	Cholesterol	Moderate	None
118	95	Cholesterol	Marked	None
119	93	Cholesterol	Marked	None
120	96	Cholesterol	Marked	None
125	45	Cholesterol	Moderate	None
111	96	None	None	None

Macroscopically, a thin, smooth lining developed within the nylon-Teflon prostheses (Fig. 1). In the animals sacrificed at 45 days this lining was so thin that the weave of the prosthesis was clearly visible. In the animals that were allowed to survive for 90 days this lining was somewhat thicker and more

opaque. On the external surface of the prosthesis a fairly marked indurated, inflammatory reaction was present, especially in the animals sacrificed at 45 days. In the animals sacrificed at 90 days this reaction was more fibrotic, with the prosthesis firmly imbedded in the fibrous tissue. In animals which were sacrificed early (40 to 50 days), comparatively little arteriosclerotic change was seen in the thoracic aorta, but plaques could be observed in the part of the abdominal aorta adjacent to the prosthesis in the region where the aorta had been traumatized during the dissection at implantation (Fig. 2).

In those animals fed cholesterol for 3 months, marked arteriosclerosis was present throughout the aorta in the form of large, confluent plaques and as smaller plaques localized about the apertures of the branch arteries (Fig. 3). It was noted that in these animals, practically without exception, the area adjoining the prosthesis (which was the area that had been traumatized during the dissection) was heavily involved in arteriosclerotic changes (Fig. 1). This predilection of arteriosclerotic changes for the traumatized area was expected and has been previously described by Prior.[9]

On microscopic examination the luminal surface of the prosthesis was found to be covered with fibrous tissue of somewhat varying thickness and comparatively low cellularity (Fig. 4). The external surface of the prosthesis was incased in fairly dense fibrous connective tissue. The host aorta exhibited lesions similar to those previously described by Prior,[9] Duff,[6] and others.[4] Intimal thickening rich in lipophages was found in animals sacrificed after 45 days. Large plaques of necrotic debris with low cellularity and few lipophages appeared in the later lesions.

Rabbit Homografts.—In the group of animals receiving rabbit homografts, every animal was found to have some arteriosclerosis in the grafted segment as well as arteriosclerosis in the immediately adjacent host aorta (Table II). The arteriosclerosis in general appeared to be more severe in the homografts than the host aorta.

TABLE II. HOMOGRAFTS

ANIMAL NUMBER	POSTOPERATIVE DAYS	DIETARY SUPPLEMENT	ARTERIOSCLEROTIC CHANGES	
			HOST AORTA	REPLACEMENT
116	51	Cholesterol	Moderate	Marked
117	96	Cholesterol	Marked	Aneurysm
122	92	Cholesterol	Marked	Marked
124	93	Cholesterol	Marked	Marked shrinkage
127	97	Cholesterol	Marked	Marked
128	91	Cholesterol	Marked	Marked
130	45	Cholesterol	Moderate	Marked
132	44	Cholesterol	Moderate	Moderate shrinkage
133	46	Cholesterol	Moderate	Aneurysm
114	94	None	None	None

Macroscopically, marked degenerative changes in the grafts were apparent. In 2 animals the graft was practically obliterated by shrinkage. In one animal this change occurred as early as 43 days. In 2 animals aneurysmal dilatation of the graft had taken place, and the circumference of the graft was approximately three times that of the host aorta.

Fig. 2.—Teflon-nylon prosthesis 43 days after implantation in cholesterol-fed animal. Note sclerotic changes adjacent to prosthesis.

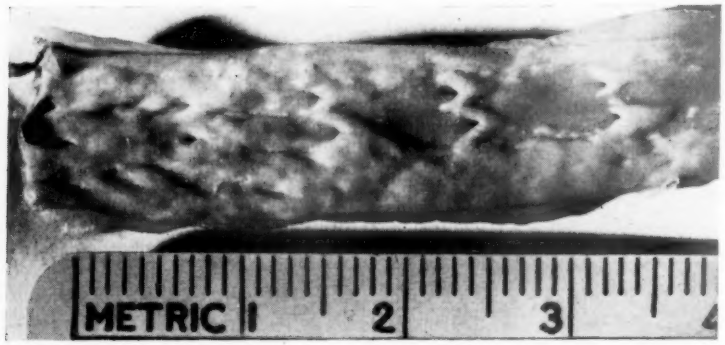

Fig. 3.—Spontaneous arteriosclerosis in thoracic aorta in animal fed cholesterol for 94 days.

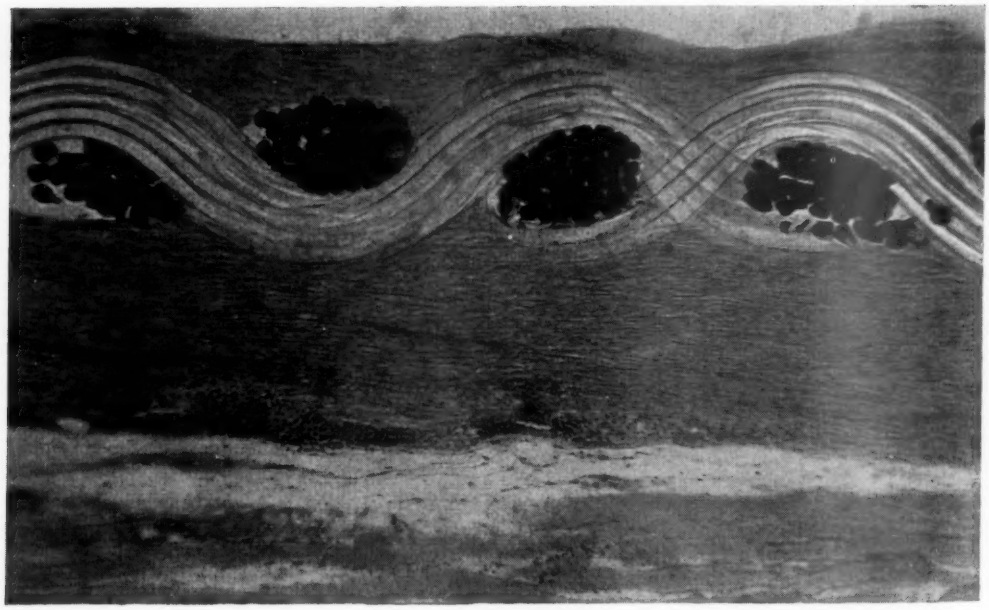

Fig. 4.—Microscopic section from wall of prosthesis in animal fed cholesterol for 96 days. Same animal as in Fig. 1.

By 43 days, marked changes were already visible in the homograft (Fig. 5), at which time none were visible in the host aorta except for minimal deposits adjacent to the graft.

In the animals which received the full 3 months of cholesterol feeding, very severe arteriosclerosis was present in the whole host aorta identical to that seen in the prosthesis group. The graft and adjoining aorta were the site of such marked changes that the suture lines were no longer clearly discernible. In most cases large confluent plaques covered the whole area (Fig. 6).

Fig. 5.

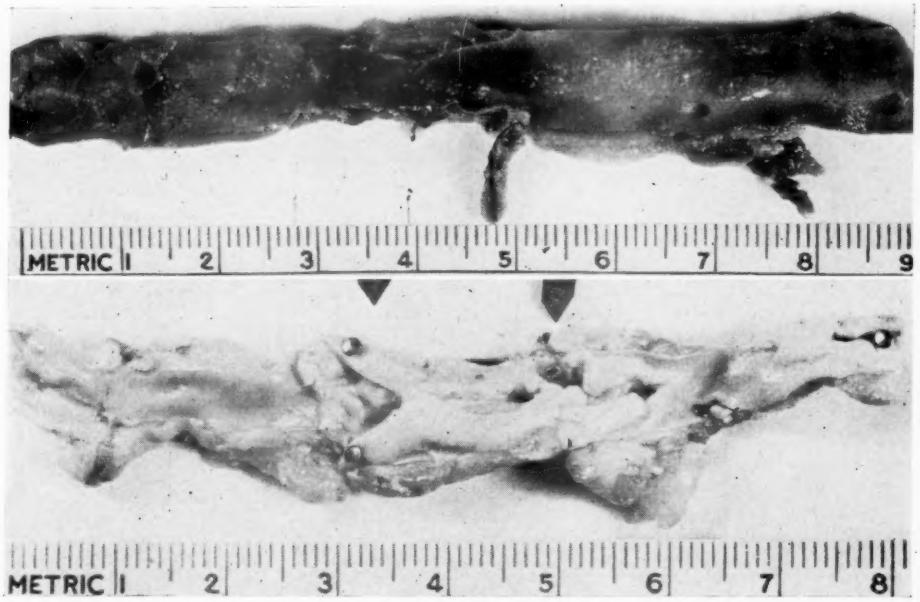

Fig. 6.

Fig. 5.—Aorta with homograft in animal fed cholesterol for 43 days. Note minimal atheroma in host aorta and marked changes in homograft.

Fig. 6.—Aorta with homograft in cholesterol-fed animal after 95 days. Suture lines are obliterated by dense changes. Homograft is completely covered by large diffuse arteriosclerotic plaques.

Microscopically, the luminal surface of the graft was comprised of the compressed fibers of the media. Near the suture lines there were layers of fibrous tissues growing in from the host aorta. The media was heavily infiltrated with lipophages and contained large necrotic plaques as early as 43 days after implantation (Fig. 7). At this stage these changes were much more marked than in the host vessel. Deposits of extracellular lipid were also present. These changes were much greater by 90 days, at which time extensive destruction of the architecture and large collections of necrotic cellular debris were found in the graft wall (Fig. 8).

COMMENT

It was impossible during the period of observation to produce any arteriosclerosis in the pseudointimal connective tissue which lined the nylon-Teflon

prostheses. Creech[4] found the same phenomenon using Orlon and nylon in dogs. It is of some significance, however, that lyophilized homografts, which are essentially nonviable vessels, used by Creech and co-workers,[5] Fisher,[7]

Fig. 7.

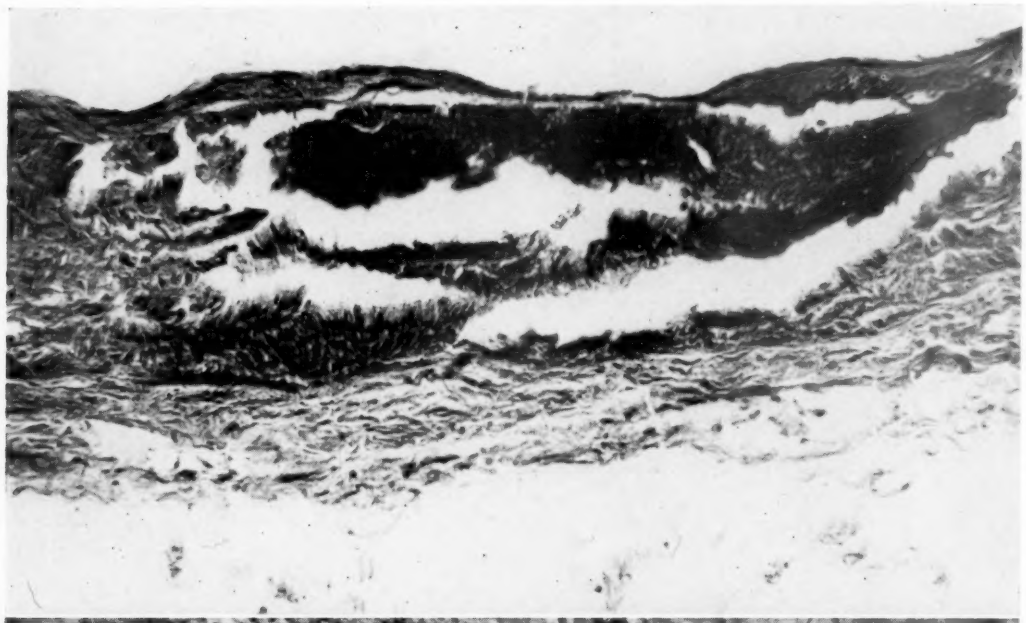

Fig. 8.

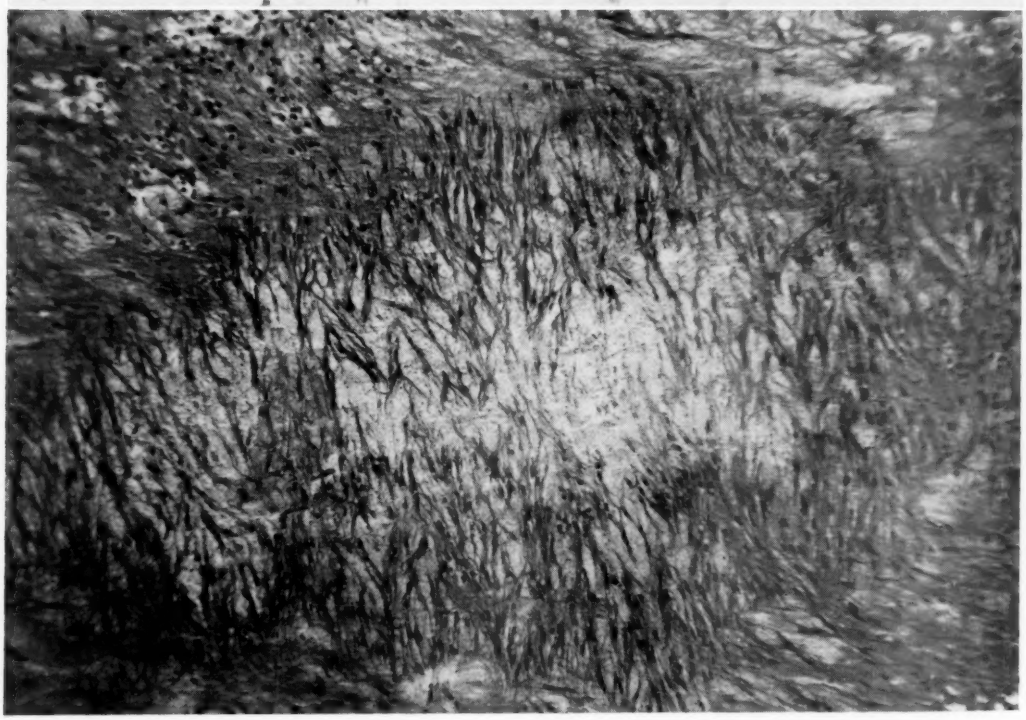

Fig. 7.—Necrotic plaque in wall in homograft in animal fed cholesterol for 43 days.
Fig. 8.—Wall of homograft in cholesterol-fed animal after 96 days. Note complete destruction of cellular architecture and replacement by necrotic debris and lipophages.

Fig. 9.

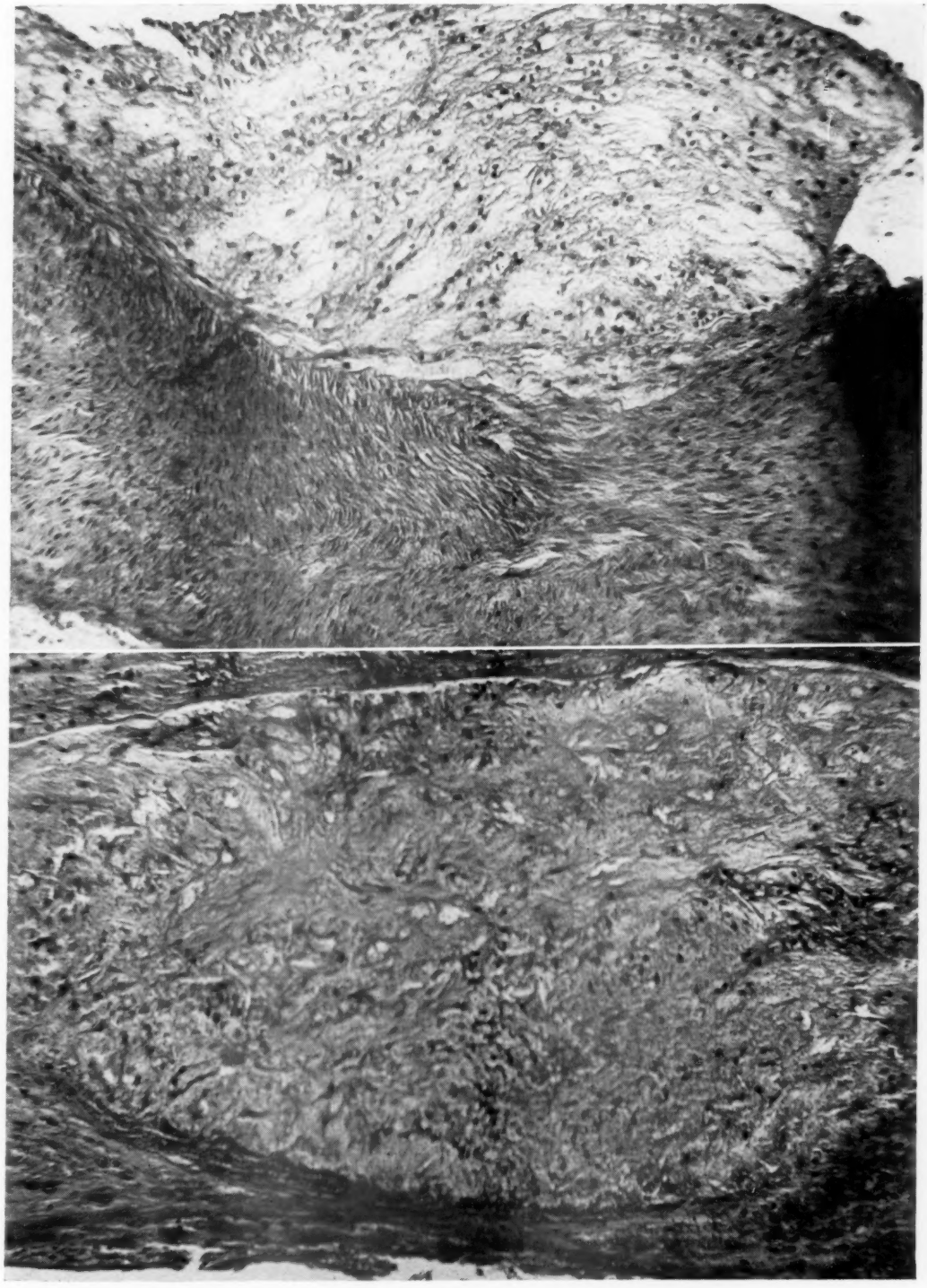

Fig. 10.

Fig. 9.—Early arteriosclerotic plaques in aorta of animal fed cholesterol for 44 days.
Fig. 10.—Sclerotic plaque in wall of aorta in animal fed cholesterol for 96 days.

and ourselves, were capable of developing arteriosclerosis. This suggests that Duff's concept that arteriosclerosis can *only* be produced in *blood vessels* may apply in greater degree to nonviable vessels than to viable ones. There may be some physicochemical component of the wall of an artery, even a dead one, which in its disintegration predisposes to arteriosclerosis. It is possible that the accelerated disintegration of a nonviable vessel is the reason for the more rapid development of arteriosclerosis. Acute trauma to the vessel wall increases the tendency to arteriosclerosis as pointed out by Prior and observed in Creech's and our preparations. It would appear from this experimental evidence that synthetic prostheses are superior to homografts in that arteriosclerosis does not develop in their walls. It is also evident that the trauma of the host wall incident to grafting is a serious incitant to arteriosclerosis.

SUMMARY

1. Nylon-Teflon prostheses and lyophilized arterial homografts have been placed in the abdominal aorta of the rabbit.

2. Arteriosclerosis was subsequently induced by the feeding of a high cholesterol diet.

3. Arteriosclerotic changes consisting of lipid deposits occurred in the host aortas of all animals. These changes were especially marked near the suture lines where the aorta was unavoidably traumatized.

4. Arteriosclerotic changes did not occur in pseudointima lining the prosthesis.

5. Arteriosclerotic changes in rabbit homografts occurred earlier than in the host aorta and to a more marked degree.

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Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

CONTRALATERAL INGUINAL EXPLORATION OF UNILATERAL HERNIA IN INFANTS AND CHILDREN

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EXPLORATION of the contralateral inguinal canal of infants and children who have clinically unilateral inguinal hernias has not been widely accepted by surgeons. A questionnaire sent to 10 large children's hospitals in the United States showed that the surgeons in 6 of these institutions do not perform a contralateral exploration. At only one institution was the opposite side routinely explored. Replies from the remaining 3 hospitals cited specific indications for the procedure. These included prematurity, left-sided hernia, hydrocele, undescended testicle, or evidence of a thickened cord on the opposite side.

Many articles in the recent literature have advocated bilateral inguinal exploration in infants and children with a unilateral inguinal hernia.[14, 15, 18] This practice has been recommended because of the high incidence of hernial sacs found on the opposite side. Other authors have stated that many of their patients have returned with contralateral hernias, but no exact figures have been cited.[4, 9] Many surgeons believe that contralateral exploration should not be done because of the possibility of injury to the spermatic cord or danger of postoperative infections.[6, 10, 12] Packard[16] believes that the low incidence of contralateral hernia in his patients returning for operation does not justify routine exploration. The problem obviously warrants further investigation.

Such an investigation was undertaken at the Children's Hospital of the East Bay. Data were derived from the following sources: (1) a comprehensive study of 708 consecutive patients with inguinal hernia admitted during a 3-year period, (2) results of contralateral exploration performed in 164 infants and children, (3) review of the records of 1,000 adult patients with indirect inguinal hernias to determine the number who had had a previous operation for hernia in childhood, and (4) results of 10- to 28-year follow-up observations on 97 patients who had had one side operated upon previously.

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Seven hundred and eight patients with indirect inguinal hernia were admitted to the Children's Hospital of the East Bay during 1954 to 1956. (Table I.) In this group inguinal hernias occurred approximately twice as frequently on the right side as on the left. Males were affected eight times more frequently than were females. The majority of the children were operated upon when they were less than 2 years of age, in accordance with the current policy of most surgeons. There were no deaths in this series of hernioplasties. Of the 708 patients, 73 had bilateral hernia at the time of admission. In the past, when the operation was customarily deferred until the child was 2 years of age or older, the reported incidence of bilaterality was approximately twice as high.[3, 8, 13, 17] Of the 73 cases of hernia which were bilateral when the patient was admitted to the hospital, the hernia had been observed to be bilateral at birth in 8 cases. A bilateral hernia was apparent within the first 6 months of life in 27 patients, the average age at the time of appearance of the second side was 10 weeks (Table II).

TABLE I. SEX, AGE, AND LOCATION OF HERNIA IN 708 PATIENTS ADMITTED TO THE CHILDREN'S HOSPITAL OF THE EAST BAY 1954 TO 1956

LOCATION OF HERNIA	NUMBER	PER CENT
Right inguinal hernia initially	423	59.7
Left inguinal hernia initially	212	30.0
Bilateral inguinal hernia initially	73	10.3
Males	627	88.6
Females	81	11.4
Infants less than 2 years old	417	58.9
Children more than 2 years old	291	41.1

TABLE II. INCIDENCE OF BILATERAL HERNIA IN VARIOUS AGE GROUPS

AGE	NUMBER	PER CENT
At birth	8	11
0 to 6 months	19	26
6 months to 2 years	19	26
2 to 14 years	27	37

Average time of appearance of second side is 10 weeks.

During the period of study, 36 patients (7.6 per cent) were admitted for repair of the opposite side. Other authors[8, 12, 16] have found that the incidence of patients returning for a contralateral hernioplasty was between 3 and 11 per cent. The initial hernioplasty was on the left side as frequently as it was on the right, although left-sided hernias occur only half as often as right-sided hernias in patients with a unilateral hernia (Table III). There was only a short interval until the contralateral hernia was observed, and in 80 per cent of the patients the second hernioplasty was performed in less than 2 years (Tables IV and V).

TABLE III. PATIENTS ADMITTED FOR OPERATION ON SECOND SIDE

SIDE	NUMBER	PER CENT
Original operation on right	19	53
Original operation on left	17	47
Total	36	100

TABLE IV. AGES OF 36 PATIENTS WHEN ADMITTED FOR REPAIR OF HERNIA ON OPPOSITE SIDE

AGE	NUMBER	PER CENT
Less than 1 month	6	17
1 to 6 months	9	25
6 to 12 months	10	28
1 to 2 years	4	11
More than 2 years	7	19

TABLE V. 36 PATIENTS ADMITTED FOR REPAIR OF HERNIA ON OPPOSITE SIDE

AGE AT OPERATION	NUMBER	PER CENT
Less than 6 months	12	33
6 months to 1 year	4	11
1 to 2 years	6	17
More than 2 years	14	39
Total	36	100

One hundred and sixty-four patients had a contralateral inguinal exploration at the time of the initial hernioplasty (Table VI). The processus vaginalis was considered patent in those patients who had a sac of 2 cm. or more in an undisturbed canal. The normal, closed processus vaginalis is readily differentiated from a false sac produced by overzealous dissection and traction on the cord. It is recognized that some of the defects close spontaneously. This is supported by the statistical evidence that more than 70 per cent of patients who are less than 6 months old have a patent hernial sac although a hernial sac is observed in only 35 per cent of children who are more than 2 years of age.

TABLE VI. INCIDENCE OF HERNIAL SACS IN 164 PATIENTS WHO HAD CONTRALATERAL EXPLORATION

	NUMBER OF CASES	NUMBER OF SACS ON SECOND SIDE	PER CENT
Right side	100	47	47
Left side	64	32	50
Less than 6 months	41	30	73.2
6 to 12 months	24	12	50.0
1 to 2 years	24	9	37.5
Over 2 years	75	28	37.3

It is evident that the sac may be present for many years, since many hernias do not appear until later in life. Of 1,000 patients with indirect inguinal hernia 242 had either a bilateral hernia or a previous operation on the opposite side. Of this group only 10 patients (4 per cent) had had their first operation in childhood. Of 100 patients with hernias who were more than 60 years of age, 33 were found to have bilateral indirect inguinal hernias. None of these patients had had a previous operation during childhood.

As shown in Table VII, 16 of 97 patients operated upon between the years 1928 and 1946 required contralateral repair. Sixty-one of these patients were observed for 10 to 20 years and 36 were observed from 20 to 28 years. Twenty-six of the patients originally had a left-sided hernia. Of the 16 patients who have had contralateral repair, 6 (37.5 per cent) initially had a left-sided hernia. This supports the belief that patients who initially have a left-sided hernia

develop contralateral hernias more frequently than those who initially have a hernia on the right side. Thirty-one patients in this group of 97 were operated upon when less than 2 years of age, which is contrary to the present practice of earlier operation. In the present series 60 per cent of the patients were less than 2 years of age. Six patients (27.5 per cent) who developed hernias on the opposite side were operated upon when they were less than 2 years of age and the remaining 10 (62.5 per cent) were more than 2 years old.

TABLE VII. OBSERVATION ON 97 PATIENTS WITH 10- TO 28-YEAR FOLLOW-UP

	CASES	PER CENT
Original hernia left side	26	27
Subsequent right hernia	6	23
Original hernia right side	71	73
Subsequent left hernia	10	14
Total requiring further surgery	16	16
Original operation under 2 years	31	32
Second operation under 2 years	6	19
Original operation over 2 years	66	68
Second operation over 2 years	10	15

DISCUSSION

The actual incidence of development of hernia on the opposite side can be determined only by long-term observations on a large number of patients, extending from the time of the original operation until death. This is obviously impractical. Anatomic studies of infants at autopsy have demonstrated that in 44 per cent of cases there was incomplete closure of the processus vaginalis.[7] In more than half of these cases the patent processus vaginalis was noted to be bilateral. In a post-mortem study of 200 adults who had not had clinical evidence of inguinal hernia, incomplete closure of the processus vaginalis was found in 47 cases. In 1942, Anson[1] observed a remnant of the processus vaginalis in 8 per cent of adult post-mortem examinations. After an extensive review of the literature, Zimmerman[21] estimated that 3 to 8 per cent of the population will eventually develop an indirect inguinal hernia.

In the present series of cases of inguinal hernia for which contralateral exploration was done, there was an inverse relationship between the age of the patient and the incidence of contralateral hernia (Table IV). In those infants operated upon within the first 6 months of life a contralateral hernia was observed in 73.2 per cent. In children more than 2 years of age a hernia on the opposite side was present in 37.3 per cent of the cases. These statistics suggest that many of the hernial sacs observed in infants will close spontaneously. Therefore, the presence of a sac is not in itself an absolute indication that a hernia will develop in the future.

During the 3-year period of evaluation, 7.6 per cent of the infants operated upon represented admissions to the hospital for repair of a hernia on the opposite side. It is apparent that during this period of study relatively few patients had to be re-admitted for repair of a contralateral hernia. In review of 1,000 patients with an inguinal hernia, 242 patients had bilateral hernias

and of these 4 per cent had had an inguinal hernia repaired in infancy. These statistics are not significant, since they do not actually represent a follow-up of a large number of patients operated upon as infants. They do indicate, however, that the number of patients operated upon as adults rarely have had a previous hernioplasty in childhood.

Bilateral exploration did not increase the mortality or morbidity rates in comparison to a unilateral operative procedure. The average period of hospitalization was 3.3 days when either unilateral or bilateral hernioplasty was performed. If no sac was found on the opposite side the operating time for the contralateral exploration was approximately one-half the time used for the initial hernioplasty. The additional degree of surgical trauma and the minimal increase in operating time did not alter the favorable postoperative course of these infants. The small number of patients returning to the Children's Hospital of the East Bay for repair of the opposite side is not a valid reason for not exploring the opposite side, since these patients may not develop a hernia on the opposite side until later in adult life. In experienced hands, the extra time required to operate upon the opposite side should not increase the mortality or morbidity, and injury to the spermatic cord structures should not occur. However, the danger associated with a second operation at a later date necessitating a second general anesthetic, would undoubtedly produce a much higher incidence of complications.

The recommendation of exploring the opposite side, therefore, will depend primarily upon the condition of the patient and the experience of the surgeon. Premature infants, patients who are responding poorly to anesthesia, or those who are being operated upon for an incarcerated hernia should not have the other side explored. If the surgeon encounters complications, is relatively inexperienced in pediatric surgery, or has spent considerable time operating upon the first side, he should not undertake exploration of the opposite side.

SUMMARY AND CONCLUSIONS

1. The controversial question concerning the advisability of exploring the contralateral inguinal canal at the time of an original hernioplasty for repair of a unilateral inguinal hernia in infants and children is restated.

2. Data derived from several sources are presented in an attempt to answer the query. (a) Results of a study of 708 consecutive cases admitted to the Children's Hospital of the East Bay for hernia repair were evaluated. (b) A contralateral exploration was performed on 164 infants and children. (c) The records of 1,000 adult patients with indirect inguinal hernia were reviewed to determine the number who had had a previous operation for hernia in childhood. (d) Ten- to 28-year follow-up investigation on 97 patients who had had one side operated upon previously were studied.

3. During the 3-year period in which 708 patients were admitted to the Children's Hospital of the East Bay for hernioplasty only 36 were admitted for repair of the second side (7.6 per cent). Contralateral exploration in 164 cases revealed a high incidence of sacs in infants less than 6 months of age

(73.2 per cent), but this figure decreased to 37.5 per cent in infants more than 2 years of age, indicating spontaneous closure of the processus vaginalis. In a review of 1,000 adults with indirect inguinal hernia, 242 of the hernias were found to be bilateral; 10 of these patients had had the initial operation as a child. A 10- to 28-year follow-up on 97 infants operated upon for unilateral inguinal hernia showed that 16 subsequently needed repair of the opposite side.

4. The high incidence of patent processus vaginalis in infants under 2 years of age does not in itself warrant routine exploration of the opposite side. Yet the small number of patients entering the hospital for repair of a second side during this study is not a true indication of the number who will subsequently need contralateral hernioplasty. Ten- to 28-year follow-up observations indicated that 16 per cent required a second operation; however, this follow-up study is much too short for true evaluation.

5. If the surgeon is skillful the mortality and morbidity should not be increased in properly selected infants and young children. However, we do not believe contralateral inguinal exploration should be done routinely but is advisable only in elective cases of patients whose general condition is excellent, on whom the anesthetic is proceeding satisfactorily, and on whom the original side has been expertly and expeditiously completed.

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LOBECTOMY FOR POSTPNEUMONIC LUNG ABSCESS IN INFANCY AND CHILDHOOD

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LUNG abscess rarely occurs in childhood. When it does, it is initiated most frequently by the aspiration of extraneous material. The aspiration generally has occurred in the past in association with operation for removal of tonsils and adenoids. Little has been published concerning the production of relatively large lung abscesses through extensive postpneumonic infectious pulmonary necrosis in infancy and childhood.

Taber and Ehrenhaft[5] in 1953, reported the experience with 128 cases of lung abscess at the hospital of the State University of Iowa. Only 5 of the 128 cases occurred during the first decade of life. The lung abscess followed tonsillectomy in 4 cases.

The availability of an increasing number of antibiotics and improvements in surgical and anesthetic techniques for pulmonary resection in recent years have brought about significant changes in the management of lung abscess.[1, 3-5] Many acute cases may be expected to respond favorably to vigorous antibiotic therapy. In the management of unresponsive and chronic cases the use of pulmonary resection has largely replaced drainage procedures.

Because of these changes in therapeutic methods and the rarity of lung abscess, especially of the postpneumonic type, in infancy and childhood, it has seemed desirable to record an experience with 4 lobectomies for lung abscess carried out on 3 patients during the first decade of life. In all of the cases the abscess was postpneumonic and in all it appeared to be due to hemolytic *Staphylococcus aureus*. The abscess in two of the cases occurred during the Asiatic influenza epidemic of late 1957 and early 1958.

CASE REPORTS

CASE 1.—The patient, a 7-week-old white male infant, was admitted to the Indiana University Medical Center on Jan. 15, 1951, because of dyspnea and cyanosis of 12 hours' duration. He had been well until 2 weeks prior to admission to the hospital. At that time, he was observed to have a respiratory tract infection and mild diarrhea. He was treated by the family physician with penicillin. He regurgitated some feedings during this period. Some labored breathing had been noticed one week prior to admission to the hospital.

He had been born by normal delivery at the end of a full-term, normal pregnancy. The birth weight was 7 pounds and 13 ounces. The mother was 29 years of age and the father 33 years of age. There were 5 siblings. There was no family history of tuberculosis or other pulmonary disorder. The patient's growth and development had been normal up to the onset of the respiratory tract infection.

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On physical examination, the patient was found to be a critically ill infant in marked respiratory distress. The temperature was 101° F. His weight was 7 pounds and 2 ounces. The positive findings were limited to the chest. Roentgen study of the chest revealed a right tension pneumothorax with a shift of the mediastinum to the left (Fig. 1). The red blood count was 3.9 million and the hemoglobin was 11.5 grams. The white blood count was 17,800 with 66 per cent neutrophils; 18 per cent of them were band forms. Nose and throat cultures, obtained at the time of admission to the hospital, both revealed the presence of hemolytic *Staphylococcus aureus*.

Chest suction was promptly started by means of a polyethylene tube which had been inserted into the right chest. However, the right lung could not be expanded due to the rapid discharge of air into the pleural space and the patient's condition remained critical. It soon became apparent that a rather sizable communication existed between the tracheobronchial tree and the right pleural space. For this reason, emergency thoracotomy was decided upon.

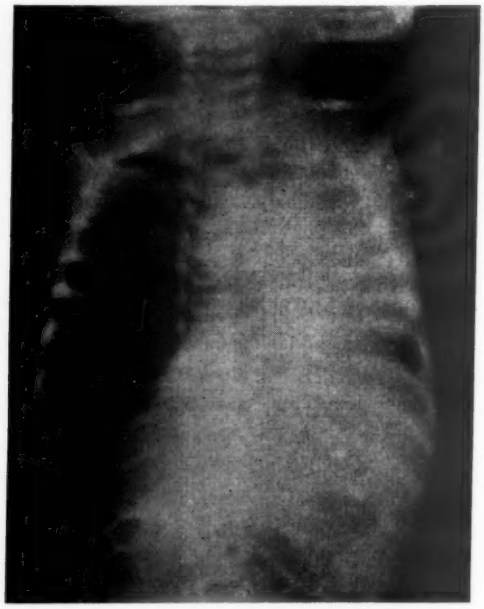

Fig. 1.—Roentgenogram of the chest in Case 1, at the time of the initial admission to the hospital, showing right tension pneumothorax.

The patient was taken to the operating room 6 hours after admission to the hospital. Under endotracheal ether anesthesia, the right chest was entered through a fifth intercostal space incision. The right lung was found to be collapsed with a fibrinous exudate covering the greater portion of all 3 lobes. It was found that a large abscess, communicating with the middle lobe bronchus and replacing virtually the entire middle lobe, had ruptured to create a sizable bronchopleural communication. Because of the size of the communication and the degree of middle lobe destruction, middle lobectomy was decided upon and was carried out by individual dissection and ligation of the hilar structures. The fibrinous exudate, covering the two remaining lobes and the parietal pleura, was removed by careful dissection. The remaining lobes were satisfactorily expanded and a solution containing penicillin was placed in the pleural cavity. A catheter was left in the chest for postoperative suction as the thoracotomy incision was closed in layers.

The infant tolerated the operation well and his condition improved immediately. The postoperative course was uncomplicated. The chest suction was discontinued 48 hours after operation and the catheter was removed. He was given 600,000 units of penicillin daily. He gained weight rapidly and was discharged from the hospital January 28.

Gross examination of the resected middle lobe revealed a large central cavity. Microscopic study of sections of the lung showed an extensive inflammatory process. Several small abscesses were encountered in some areas. A good portion of the lung parenchyma was replaced by scar. There was considerable compression and atelectasis of the remaining alveoli. There was no histologic evidence of tuberculosis and no acid-fast bacilli could be found on direct smear. However, an atypical acid-fast organism was identified later from this material on culture. Subsequent guinea pig inoculation studies were negative for tuberculosis.

Because of the demonstration of this atypical acid-fast bacillus on culture, the patient was readmitted to the hospital on February 6 for further study. All the bacteriologic studies relative to tuberculosis and the tuberculin test were negative. The infant was asymptomatic at the time of this admission and the roentgen study of the chest was interpreted as being normal with respect to the remaining pulmonary tissue. Chest roentgenograms were made on all other members of the infant's family and all were interpreted as normal. The patient remained asymptomatic until February 14, at which time intermittent elevations of temperature to as high as 102° F. were noted. Roentgen study of the chest at this time showed consolidation in the area of the right upper lobe (Fig. 2). Thoracentesis in the area of roentgen opacity was carried out on February 20 and a small amount of tenacious purulent material was obtained. Culture of this material revealed hemolytic *Staphylococcus aureus,* coagulase positive. Despite vigorous antibiotic therapy with penicillin, 800,000 units per day, the consolidation persisted and an area suggesting an abscess cavity became more prominent.

On March 1, the patient was taken to the operating room and the right chest was reopened through the old incision. There was no evidence of empyema. The pleural space was entirely obliterated. The right upper lobe was atelectatic and contained a large abscess. The lower lobe was normal in appearance. Right upper lobectomy was decided upon and was carried out with individual ligation of the hilar structures. A catheter was left in place for postoperative chest suction and the thoracotomy incision was closed in layers.

The abscess cavity was identified on gross examination of the resected upper lobe. There was no evidence of bronchial communication with the abscess cavity. A microscopic examination of the area near the cavity showed necrotic tissue surrounded by a rather heavy inflammatory infiltrate. Considerable atelectasis also was encountered. There were no tubercules or histologic evidence to suggest tuberculous infection. The sections from the right upper lobe were similar to those from the right middle lobe with the exception that no smaller abscesses were found in the upper lobe.

The patient tolerated the operation well and the postoperative course was essentially uncomplicated. Chest suction was maintained for 2 days after operation. Antibiotic therapy was continued. He was discharged from the hospital on March 18. His growth and development have been normal since his release from the hospital. There has been no recurrence of respiratory tract difficulties. The last roentgenogram of the chest, taken 2 years after the last operation, showed good expansion of the remaining pulmonary tissue in the right chest (Fig. 3).

CASE 2.—The patient, a 16-month-old white female, was admitted to the Indiana University Medical Center on Nov. 25, 1957, because of bilateral pneumonia and hyperpyrexia of approximately 2 weeks' duration. The patient had been well until 4 weeks prior to her admission to the hospital. At this time she was noted to be somewhat lethargic with a mild nasal discharge, cough, and temperature elevation. She was managed with penicillin and an oral sulfa preparation with prompt apparent recovery. Approximately 2 weeks prior to her admission to the hospital, her lethargy, cough, and fever returned. She was admitted to the hospital of a community near her home where roentgen study of her chest revealed bilateral pneumonitis. She was treated more vigorously with broad-spectrum antibiotics

Fig. 2.—Roentgenograms of the chest in Case 1, at the time of the second admission to the hospital, showing a normal-appearing chest (*A*), the occurrence of right upper lobe staphylococcal pneumonic consolidation (*B*), and the development of a postpneumonic lung abscess (*C*).

and she improved briefly. Shortly before her transfer to the Indiana University Medical Center, she experienced a marked exacerbation of the pneumonic process and her temperature rose to 106° F.

The patient had been born by normal delivery at the termination of a normal pregnancy. Her birth weight was 8 pounds and 2 ounces. Her growth and development had been normal. She had been in good health until the onset of the present illness with the exception of an episode of pneumonia in January, 1957. There was no family history of tuberculosis or other chronic pulmonary disorder. The parents and 2 siblings were living and well. The youngest sibling, 4 years of age, had suffered from frequent episodes of upper respiratory tract infection.

On admission to the hospital, the patient was found to be acutely ill and quite irritable. Her temperature was 105.4° F., the pulse 134, and the respirations 36. Râles were heard in the inferior areas of the left chest. A roentgenogram of the chest at this time showed a pneumonitis of the left lower lobe with a homogeneous area of infiltration along the left border of the heart. The red blood count was 4.6 million and the hemoglobin 12 Gm. The white blood count was 24,300 with 72 per cent neutrophils. A throat culture revealed the presence of hemolytic *Staphylococcus aureus*. Tuberculin and histoplasmin skin tests were negative.

Fig. 3.—Chest roentgenogram in Case 1 taken 2 years after the last operation. Satisfactory expansion of the remaining pulmonary parenchyma in the right hemithorax is shown.

The early hospital course was rather stormy. Daily temperature elevations to as high as 104 and 105° F. continued for 9 days. She was given penicillin and Achromycin. The temperature had returned toward normal on December 3. A roentgenogram of the chest at this time revealed an area of increased density in the lower left lung field with an air fluid level. The cavity was seen on the lateral view to occupy the posterior portion of the lower lobe. It was estimated to measure approximately 4 by 4 cm. The remaining lung fields appeared clear. A tentative diagnosis of postpneumonic lung abscess was made.

The patient was taken to the operating room on December 5. Under general, endotracheal anesthesia, the left chest was opened through a sixth intercostal space incision. An abscess was found to occupy a rather large portion of the left lower lobe. The lobe was adherent to the posterior chest wall. The lobe was dissected free from the surrounding structures and the lobectomy was carried out by individual ligation and division of the hilar vessels. Interrupted silk sultures were used to close the bronchial stump. There was some discharge of purulent material into the tracheobronchial tree during the operation. This had not

Fig. 4.—Roentgenograms of the chest in Case 3 showing bilateral pneumonitis (*A*), left lower and middle hemithorax consolidation and abscess formation (*B*), and upward displacement of the bronchial tree on bronchography (*C*).

occurred prior to operation. A solution containing 100,000 units of penicillin was injected into the pleural cavity and the thoracotomy incision was closed in layers. A catheter was left in the chest for postoperative suction.

Gross examination of the resected left lower lobe revealed that much of the parenchyma was replaced by a cavity lined with a greyish-yellow, fibrinopurulent exudate. Adjacent areas were noncrepitant and atelectatic. No definite communication could be established between a bronchus and the abscess cavity. No smaller abscesses were identified. Culture of the material from the abscess cavity produced a pure culture of hemolytic *Staphylococcus aureus,* coagulase positive. On histologic study, the abscess cavity was found to be lined by a fibrinopurulent exudate which rested on a granulation tissue base surrounded by a thin fibrous wall.

The patient tolerated the operation well and the postoperative course was essentially uncomplicated. The left upper lobe remained well expanded. Chest suction was maintained for 2 days following operation. Antibiotics were continued with Achromycin and Erythromycin. The patient was discharged from the hospital on December 18. Except for the occurrence of a wound abscess from which hemolytic *Staphylococcus aureus* was cultured, she has done well since her release from the hospital. The abscess responded to antibiotics and local measures.

Case 3.—The patient, a 9-year-old white girl, was admitted to the Ball Memorial Hospital on Feb. 17, 1958, because of severe exacerbation of an acute respiratory tract infection of 2 weeks' duration. Two other members of the patient's family had suffered from attacks of influenza just prior to the onset of the patient's illness. The symptoms associated with the first week of the patient's respiratory infection were rather mild. However, during the second week, they became more severe. She experienced some abdominal discomfort and nausea, generalized aches and pains, and intermittent elevations in oral temperature to 101° F. Her cough became more severe and the sputum, at times, became blood tinged. She complained of chest pain and difficulty in getting her breath. During the evening of the day prior to her admission to the hospital, she experienced a marked exacerbation of symptoms and temperature rose to 106° F. orally.

There was little of medical significance in the patient's past history. She had been born a mild spastic and a minor orthopedic operation had been carried out on her left foot at 5 years of age. She had had measles, chicken pox, and whooping cough. She seldom contracted respiratory tract infections and had rather consistently enjoyed good health.

The patient's mother and father were living and well at 28 and 30 years of age, respectively. Siblings, 6 years and 4 months of ages, were normal and of good health. There was no family history of congenital malformations or of tuberculosis or other pulmonary disorders.

On admission to the hospital, the patient was found to be an acutely ill-appearing young white girl. She complained of chest and back pain and of difficulty in breathing. She coughed frequently. Her weight was 85 pounds, temperature was 100.2° F., pulse 128 per minute, and respirations 44 per minute. The positive findings were largely limited to the chest where râles and evidence of consolidation were encountered throughout both lower lung fields. Roentgen study of the chest at this time suggested the presence of a bilateral pneumonic process, most marked on the left (Fig. 4).

The admission hemoglobin was 13 Gm. and the red blood count was 4.4 million. The white blood count was 41,200. Differential examination of the blood smear revealed 2 per cent eosinophils, 1 per cent basophils, 15 per cent lymphocytes, 1 per cent monocytes, and 81 per cent neutrophils. Twenty-eight of the 81 per cent neutrophils were band forms. Marked toxic granulation of the neutrophils was observed. The urine examination was within normal limits. The blood serology was negative. Tuberculin and histoplasmin skin tests were negative and the sputum was negative for tubercle bacilli. On throat culture, hemolytic *Staphylococcus aureus, Diplococcus pneumoniae,* and hemophilus influenza were obtained.

The patient was treated initially with 1.6 million units of penicillin daily. Eight days later, Chloromycetin, 1.5 Gm. per day, was added. Although the patient appeared to be improving clinically, intermittent temperature elevations to as high at 104° F. continued during the first 10 days of hospitalization. Following this period, the temperature remained within normal limits. Repeated roentgen and physical examination of the chest revealed prompt clearing of the pneumonic process in the right lung. However, the roentgen appearance of the left chest failed to improve. A large, homogeneous mass appeared to have developed in the lower portion of the left hemithorax. In one area there was a suggestion of several fluid levels.

The patient was seen in consultation on March 13 because of the failure of the disease process in the left chest to resolve. A tentative diagnosis of lung abscess had been made. On March 17, bronchoscopic examination and bronchography were carried out under general anesthesia. No purulent material was encountered in the tracheobronchial tree and there was no evidence of a foreign body. Bronchography with Dionosil demonstrated rather marked upward and anterior displacement of the left bronchial tree. There was no evidence of intrinsic abnormality of the left bronchial system and no evidence of bronchial communication with the displacing mass (Fig. 5).

Fig. 5.—Bronchogram in Case 3 showing upward bronchial displacement and the absence of communication of the bronchial tree with the massive abscess cavity.

The patient was taken to the operating room on March 24. Under general endotracheal anesthesia, the left chest was entered through a sixth intercostal space incision. A large, tense mass was found to occupy a significant portion of the left hemithorax. This, on further dissection, was presumed to be a massive abscess of the left lower lobe. The mass was densely adherent to the chest wall, the diaphragm, and the mediastinum. An 18-gauge needle was inserted into the mass and approximately 500 c.c. of creamy, purulent material was withdrawn. It was found that this massive abscess had virtually replaced the entire left lower lobe. Some loculation was encountered in the superior portion of the mass. The lower lobe remnant, which made up the wall of the abscess, was dissected free from the surrounding structures and a left lower lobectomy was carried out. The arteries to the superior and basilar segments and the inferior pulmonary vein were individually ligated and divided. The superior segment bronchus and the basilar segment bronchus were

individually divided and closed with interrupted sutures of 4-0 silk. A pleural flap was used to cover the bronchial stumps. The left upper lobe parenchyma was free of involvement. Some adhesions between the upper lobe and the chest wall were divided to permit normal expansion of the lobe. A small amount of streptomycin-penicillin solution was left in the chest at the time of closure. The thoracotomy incision was closed in layers and a catheter was left in the left chest for postoperative suction. The patient tolerated the procedure quite well.

The postoperative course was uneventful. Chest suction was maintained for 2 days following operation. The left upper lobe remained well expanded. The patient was afebrile throughout the postoperative period and her recovery was prompt. She was discharged from the hospital on April 15, 12 days after operation. She has remained well since release from the hospital.

No growth could be obtained on culture of the material aspirated from the abscess cavity at operation. The gross and microscopic pathologic findings were consistent with a massive abscess of the left lower lobe. There was no communication with the bronchial tree and no evidence of a foreign body. The walls of the abscess were composed of fibrous and granulation tissue.

DISCUSSION

The rarity of lung abscess in infancy and childhood may be illustrated by the finding that pulmonary resection for lung abscess was required in only 2 patients (Cases 1 and 2) on an active pediatric surgical service during an 11-year period (1947 to 1958) at the Indiana University Medical Center. In both of these cases, the resection was required for abscesses of the postpneumonic type. The infrequent occurrence of pulmonary abscess in this group has been emphasized in recent years by Lindskog and Liebow.[2]

The initial symptoms in all 3 of the cases reported here were of respiratory tract infection with fever of 2 to 4 weeks' duration prior to admission to the hospital. The ages of the patients ranged from 7 weeks to 9 years of age. In none of the patients was there any discharge of purulent material from the tracheobronchial tree prior to operation. Two of the lung abscesses occurred during an influenza epidemic regarded to be of the Asiatic type. In both patients the respiratory tract infection was characterized by remissions and exacerbations and, in both, marked hyperpyrexia to as high as 106° F. occurred prior to the admission of the patient to the hospital. Both patients were shown radiologically to have extensive bilateral pneumonitis prior to the localization of the inflammatory process to one lobe of one lung, the left lower lobe in both cases. One patient was admitted to the hospital during the early weeks of life because of marked respiratory distress due to tension pneumothorax. The tension pneumothorax had been produced by rupture into the pleural space of a large abscess which also developed a sizable communication with the tracheobronchial tree through the bronchus supplying the involved lobe.

The diagnosis in these cases was largely established through repeated roentgen studies of the chest. The prior occurrence of bilateral or localized pneumonic infiltration was demonstrated radiologically in all of the abscesses, except the one in which the initial roentgenogram showed a tension pneumothorax. The roentgen suggestion of cavitation was apparent to some degree in all of the unruptured abscesses. Two of the abscesses occurred nonsimultaneously in one of the patients, the youngest. Bronchoscopy and bronchography

were carried out on only one of the patients. In this patient, the oldest, a massive left lower lobe abscess was shown to have no communication with the tracheobronchial tree and to produce marked upward displacement of the bronchi to the left upper and lower lobes.

The white blood count was found to be significantly elevated in all of the patients on admission to the hospital. Throat cultures revealed the presence of hemolytic *Staphylococcus aureus* in all 3 patients. Hemolytic *Staphylococcus aureus* was cultured from 3 of the 4 abscesses. No growth was obtained on culture of purulent material from the massive left lower lobe abscess in Case 3, this after 5 weeks of intensive therapy with Chloromycetin. An earlier respiratory tract culture in this case had demonstrated the presence of hemolytic *Staphylococcus aureus*. *Diplococcus pneumoniae* and hemophilus influenza had also been isolated from the respiratory tract of this patient.

Two of the abscesses involved the left lower lobe, one the right middle lobe, and one the right upper lobe. In all, the area of abscess involvement was limited to a single lobe and generally produced near-total destruction of the involved lobe. All 4 abscesses were managed successfully by lobectomy. The period of time from the onset of symptoms to lobectomy was 2 weeks in each of the abscesses in Case 1 and 9 weeks in both Case 2 and Case 3. The age of the patient at the time of each lobectomy was 7 weeks, 13 weeks, 16 months, and 9 years, respectively. There was no early or late mortality. Neither empyema nor bronchopleural fistula occurred following operation. The only complication was the development of a wound abscess in Case 2 after the release of the patient from the hospital. Hemolytic *Staphylococcus aureus* was cultured from this wound abscess. It responded satisfactorily to antibiotics and local measures. A second lung abscess in the same hemithorax occurred one month after the initial lobectomy in Case 1. There was no evidence of involvement of the second lobe in this case either at the time of the first operation or on early postoperative roentgenograms taken up to 3 weeks following operation. Hemolytic *Staphylococcus aureus* was cultured from both abscesses.

All 4 of the abscess cavities were relatively large ones and occupied the greater portion of the involved lobes. The remaining pulmonary tissue was compressed and atelectatic. The cavities all were lined with granulation and fibrous tissue. A bronchial communication was found in only one abscess cavity. This cavity had also acquired a communication with the pleural space. Several considerably smaller abscess cavities also were discovered in two of the lobes. The largest cavity occurred in Case 3. The massive left lower lobe abscess in this case occupied a large portion of the left hemithorax and produced marked upward displacement of the bronchi to the left lung.

SUMMARY

1. Lung abscess, especially of the postpneumonic type, rarely occurs in infancy and childhood.

2. An experience with 4 lobectomies for postpneumonic pulmonary abscess in 3 patients during infancy and childhood is reported. The lobectomies were

carried out at 7 weeks, 13 weeks, 16 months, and 9 years of age, respectively, without mortality or significiant postoperative complication and with good results.

3. Hemolytic *Staphylococcus aureus* was cultured from the respiratory tract in all 3 patients and from the contents of 3 of the 4 abscess cavities. No growth could be obtained from the contents of one large cavity after 5 weeks of intensive antibiotic therapy.

4. All of the abscess cavities were quite large and all were lined with granulation and fibrous tissue. A communication with the tracheobronchial tree was demonstrated in only one abscess. This abscess cavity also communicated with the pleural space, producing a tension pneumothorax.

5. In two of the cases, the pulmonary abscess occurred during an epidemic of influenza, Asiatic type. In both cases, bilateral pneumonitis had been demonstrated roentgenologically prior to the formation of the abscess. Both cases were characterized initially by remissions and exacerbations of respiratory tract infection and episodes of marked hyperpyrexia.

6. In one case, emergency lobectomy was necessary in a 7-week-old infant because of tension pneumothorax due to communication of the abscess with both the bronchus and the pleural space. A second, noncommunicating lung abscess occurred in this infant one month after the initial operation and was also managed successfully by lobectomy.

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CONGENITAL CYSTIC DILATATION OF THE COMMON BILE DUCT

Special Reference to Radiographic Studies

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CHOLEDOCHAL cyst or congenital cystic dilatation of the common bile duct is one of those rare conditions which is the frequent subject of clinical reports. Tsardakas and Robnett,[17] in a recent review, analyzed reports of 235 cases. However, in 17,381 operations on the biliary system, performed at the Mayo Clinic before 1926,[5] there were only 2 cases of choledochal cyst, and in 757,000 admissions to the Presbyterian Hospital in New York City there were only 2 cases.[16] In the Whittington Hospital in London there was but one case in 26,520 admissions.[17] From 1923 to 1954 at Cleveland Clinic Hospital there were 2 cases in 192,507 admissions.[17]

THE NATURE OF THE ANOMALY

Anatomic Characteristics.—The deformity consists of a circumferential dilatation of the entire common bile duct or of a segment of it, with occasional extensions involving the cystic, hepatic, or common hepatic ducts. The dilatation is usually reported to commence some 2 cm. above the duodenum.[17] However, in some instances, the cystic mass may extend down to the entrance of the common bile duct into the duodenal wall. There is a single report of an intraduodenal dilatation of the common bile duct which was considered to be a choledochal cyst, but it actually may have been an enterogenous cyst.[14] Gross[3] notes that in rare instances the pancreatic ducts may open directly into the choledochal cyst. Of considerable significance from the standpoint of the etiology and mechanism of production of these cysts is the fact that the common duct between the cyst and the duodenum is commonly no larger than normal, and at times the same is true for the ducts on the hepatic side of the cyst. The gall bladder is usually not dilated in association with such cysts. Only exceptionally does a cyst occur as a diverticulum or saccular structure attached to an otherwise normal common duct. The usual choledochal cyst is actually an aneurysmal dilatation of the duct.

The cysts may vary in size from small ones several centimeters in diameter to enormous cysts distending the abdomen. Reel and Burrell[11] describe a cyst containing 8 L. of bile.

The cyst wall ranges in thickness from 2 to 10 mm. Histologically the wall is composed of fibrous tissue. The lining epithelium has varied from cylindrical to cuboidal with accompanying irregular deposition of bile pigment. There

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are occasionally elastic fibers and smooth muscle elements. A rare mucous gland may be found. If there has been marked inflammation in the cyst, no epithelium may be detectable.

Theories of Origin.—With few serious dissents the consensus is that the cyst formation is on a congenital basis. General agreement goes no further. Rostowzew[13] described a very large cyst in a 13-year-old girl in whom the undilated distal common duct passed obliquely through the lower wall of the cyst creating a valvelike effect. The cystic duct was protected by a valvelike fold, and this duct and the gall bladder were not dilated. The hepatic duct communicated freely with the cyst and was dilated. The patient reported by Arnolds,[1] also a 13-year-old girl, demonstrated a hepatic duct and cystic duct greatly dilated and a small effluent common duct coursing obliquely through the cyst wall. Such obstructive mechanisms have not been observed by others, and, if they were the usual mechanism of formation, one would expect the gall bladder and hepatic ducts to be dilated, which is rarely the case.

Some feel that there is a congenital stenosis of the lower portion of the common bile duct, resulting in obstruction and dilatation.[15] This argument runs afoul of the same facts as the previous explanation.[16] Achalasia of the sphincter of Oddi has been mentioned as a possible cause.[19] Like the other theories accounting for the cystic dilatation on the basis of obstruction, this does not explain the fact that the dilatation is usually limited to the cyst. Various other obstructive mechanisms have been impugned, such as valve formation from a redundant duct membrane, obstruction by previous cholangitis, and so forth.[11] Further, these suggestions of an obstructive etiology do not explain the fact that the jaundice is usually intermittent and infrequent.[14] A number of authors have compared the deformity to congenital "idiopathic" hydronephrosis or ureterectasis. This would be presumed to be a developmental anomaly due to weakness of the common duct wall, with dilatation under normal intraductal pressure or possibly under increased pressure secondary to obstruction.[3] We have seen no anatomic studies to substantiate such a thesis, and the cyst wall is usually, if anything, somewhat thicker than the wall of the normal bile duct.

The facts that frequently the duct proximal and distal to the anomaly is not dilated, that the gall bladder is usually not distended, and that there is rarely any satisfactorily demonstrable distal obstruction as well as the fact that jaundice is intermittent all tend to eliminate obstruction as the basic etiologic factor. Even an obstruction during intrauterine life should cause dilatation of the hepatic ducts as well. We are left with the unsatisfactory explanation that in most cases this is a primary local anatomic malformation. The present low mortality of the condition indicates that few complete specimens will be available for anatomic study.

Clinical Features.—The malformation is most common in females, occurring 3 to 4 times more commonly than in males (74 per cent of Tsardakas and Robnett's 232 cases were females). The condition, although congenital, is usually not manifest at once. Gross,[3] in a survey of 128 patients, found that 44 were

hospitalized before the tenth year of life, 31 in the next decade, 32 in the third decade, 11 in the fourth decade, and 10 thereafter. Eighty per cent of Tsardakas and Robnett's patients had had cysts discovered before they were 30 years old.

The clinical manifestations consist of the classical triad of attacks of pain, a palpable mass, and jaundice. The figures for incidence of these symptoms given below are from Tsardakas and Robnett.[17]

Pain (63.4 per cent): The pain is described as crampy or colicky, sometimes merely as a heavy pressure or fullness, and occasionally as a vague feeling of discomfort. It is usually localized in the right upper quadrant or epigastrium and occasionally at the level of the umbilicus. Nausea and vomiting may be associated with this pain. Grove[4] suggests that vomiting occurs when the cyst enlarges sufficiently to press upon and obstruct the duodenum. As in our Case 3, pain may be the only symptom.

Mass (72 per cent): Gross[3] reports the highest incidence of a palpable mass—90 per cent of his cases. The mass is usually felt in the right subcostal region just below the liver but may be displaced to the left of the midline by the right lobe of the liver or may be so large as to fill the entire upper abdomen.

Jaundice (69 per cent): In Gross's[3] cases, 90 per cent were jaundiced. The jaundice is characteristically intermittent but not invariably so. It is generally associated with acholic stools and dark urine.

Chills and fever: Chills and fever may occur during acute obstructive episodes and are taken to represent bouts of infection of the cyst and ascending cholangitis.

Pancreatitis: Pancreatitis has been reported in association with the attacks of pain.[17] In our Case 3 which was in most respects a fairly typical case, the attacks of recurrent pain were almost certainly attacks of pancreatitis and this may be the mechanism of the crises more frequently than has been recognized.

Repeated attacks: Repeated attacks may apparently result in biliary cirrhosis with attendant splenomegaly, hypersplenism, anemia, purpura, and hematemesis from varices.

Characteristic of the condition is its chronicity and the periodicity of the attacks over long periods of time, if the condition is left uncorrected.[3]

DIFFERENTIAL DIAGNOSIS

Diagnosis is apparently not readily made. In the series reported by Gross[3] the average duration of symptoms before accurate specific diagnosis was 3 years. At various times the condition has been confused with almost every other cause of abdominal pain, mass, or jaundice. Many of the children, like our Patients 2 and 3, had previous appendectomies.

Abdominal Neoplasm, Particularly Wilms's Tumor or Neuroblastoma.—In these instances the abdominal mass is usually hard, nodular, and neither cystic nor smooth like choledochal cyst. The jaundice in these conditions is terminal

and episodic attacks do not occur. Most such neoplasms run a rapid course, but in an occasional case a mass may have been present for a long enough time to raise doubt as to the malignancy of the basic process.

Cholelithiasis.—Pain and jaundice may occur in children with cholelithiasis as in adults, but cholelithiasis is extremely uncommon in children except in association with one of the congenital hemolytic anemias. Radiographic study will usually make the specific diagnosis of cholelithiasis. Rare as cholelithiasis is in children, hydrops of the gall bladder is rarer still but, at times could present a confusing picture. Cholelithiasis, like the condition under consideration, is likely to be productive of chronic and intermittent symptoms.

Pancreatitis.—This condition is rare in children. An associated pancreatitic pseudocyst, which might produce a mass liable to confusion with a choledochal cyst, would be rarer still. More confusing is the fact that a choledochal cyst may present with attacks of pancreatitis. Radiologically a pseudocyst should be readily separable from a choledochal cyst. Whereas the latter displaces the duodenum medially and caudally, a pseudocyst lying in the duodenal loop spreads the loop apart and tends to displace the stomach anteriorly.

Mesenteric Cysts, Enterogenous Cysts, and Other Cystic Intra-abdominal Malformations.—Enterogenous cysts and other cystic intra-abdominal malformations must be considered. In general, these are movable and do not cause jaundice.

Other Cysts.—Hemangiomas of the liver, other cystic hepatic tumors, echinococcus cysts, and renal cysts may all present cystic swellings with attacks of pain but usually without jaundice.

Congenital Atresia of the Bile Ducts.—In this condition the jaundice is present shortly after birth and is unremitting. By contrast, only 5 per cent of the choledochal cysts in Gross's[3] patients were symptomatic before the children were 6 months of age. In choledochal cysts the jaundice is intermittent, and in biliary atresia a cystic mass is ordinarily not felt or present.

RADIOLOGIC CHARACTERISTICS

We have been particularly interested in the radiologic study of these lesions and in their treatment.

Previous case reports have described a variety of roentgenographic features. On the plain film there will be noted a rounded soft tissue mass in the right upper quadrant. The renal outline in such cases is frequently visible through the shadow of the cyst and discrete from it. An upper gastrointestinal series has usually shown the duodenum to be displaced medially, inferiorly, and anteriorly.[2, 8, 10] When the cyst has been large enough it has displaced the stomach downward and to the left. Study of the kidneys by intravenous pyelography has at times shown some downward displacement of the right kidney by the mass, and in at least one instance the right ureter has been found to be compressed by the choledochal cyst, producing a hydroureter and hydronephrosis.[20] A barium enema may show the hepatic flexure displaced downward and anteriorly, and with large cysts the ascending colon may be found to be lifted forward as well.

Oral cholecystography and intravenous cholangiography have been reported usually as failing to visualize a choledochal cyst. Mosely[9] in a review of over 200 cases in 1957 reported what he considered to be the first visualization of a choledochal cyst by oral cholecystography. Perhaps it is significant that his patient was not jaundiced at the time. Grove[4] in 1957 also reproduced a very clear oral cholecystogram showing visualization of both the cyst and of the gall bladder. Wright,[20] in 1935, had previously demonstrated the gall bladder in such a patient although the cyst had not been demonstrated by the oral cholecystography.

More direct approaches at radiographic demonstration have been made at times. Kjellberg[7] in 1947 in a patient 7 years old was able to aspirate the cyst by percutaneous puncture and inject 20 c.c. of Per-Abrodil (a water-soluble contrast material). He demonstrated the gall bladder and a cyst of the common bile duct as large as a child's head.

In 1948 Urwitz[18] by a similar technique in a patient 9 years old demonstrated by percutaneous injection of Per-Abrodil using x-ray control a choledochal cyst with the gall bladder as an appendage to the cyst.

In 1957 Rheinlander and Bowens[12] during an operation injected Diodrast into the cyst and demonstrated the cyst and the dilated common duct.

Keith, Rini, and Martin[6] at operation for cholelithiasis and choledocholithiasis in a patient 43 years old injected the cyst with radiopaque material and demonstrated a cystic dilatation of the common duct and stenosis of the postcystic portion of the common duct. The patient had 3 stones and muddy sediment in the cyst. This is a unique finding in such cases. The stenosis may be considered a consequent of repeated infection rather than the cause of the cystic dilatation. In another case reported by Keith and associates[6] the gall bladder was drained at operation and subsequent injection of contrast material through the cholecystostomy tube demonstrated the cyst and reflux into the pancreatic duct.

TREATMENT

Three methods of treatment have been employed.

Aspiration.—This is more a diagnostic rather than a therapeutic technique. External drainage, or the so-called marsupialization, certainly should never be attempted. As the treatment of choice in an earlier day, it carried a prohibitive mortality.

Excision of the Cyst.—This might appear to be the most definitive treatment. However, in cases of true congenital dilatation of the common duct, excision requires a formidable operation and poses a problem in reconstruction with danger of stricture of the end-to-end anastomosis of the common duct or of the anastomosis of the proximal common hepatic duct to the duodenum.

Anastomosis Between the Cyst and the Intestinal Tract.—This has become the standard method of treatment. As might be supposed, every conceivable type of anastomosis has been employed.

Cholecystogastrostomy and cholecystoduodenostomy anastomosing the gall bladder to stomach or duodenum: This is an indirect method of relief and has little to commend it.

Cystoduodenostomy, cystogastrostomy, or direct anastomosis of the cyst to the duodenum or stomach: This is technically extremely simple and the anastomosis can be made any desired size. We feel that in the cysts which are not extremely large and which lie principally behind the duodenum, to which they are densely adherent, a direct anastomosis between the duodenum and the cyst is the preferred operative procedure. The structures are usually so firmly adherent that, at most, only one layer of sutures is necessary for the posterior suture line.

Roux-en-Y anastomosis between the jejunum and the cyst: This is the operation of choice whenever it is feasible and it is generally feasible only in the very large cysts. In the small cysts which are essentially retroduodenal, it is to be feared that the long limb of the Roux anastomosis coming across the duodenum might compress and obstruct the latter.

The results of these anastomotic procedures have on the whole been quite satisfactory. The direct anastomosis to the duodenum has the disadvantage, as demonstrated in Fig. 4, that at first, material from the duodenum can find its way into the cyst. On the other hand the nature of the anomaly and its anatomic situation impose certain constraints upon the surgeon, and in the cysts which are largely retroduodenal there appears to be little other choice.

There would appear to be no uniformity of opinion as to the necessity for simultaneous cholecystectomy. We did not perform it in the 2 instances in which we performed a direct anastomosis between the cyst and the duodenum. This would appear to be in accord with the general practice, and there have appeared as yet no reports of consequent disease in the gall bladder. However, in the copious literature dealing with choledochoenterostomies of various types in connection with pancreatitis and pancreatic cysts, there are numerous recommendations for cholecystectomy at the time of such operations lest the gall bladder develop serious consequences of infection attendant upon regurgitation of material from the intestines into the common duct.

CASE REPORTS

CASE 1.—S. H. (J. H. H.—A79218), a 3½-month-old female infant, was brought to the hospital with a distended abdomen and an easily palpable cystic mass filling the epigastrium and most of the right side of the abdomen to the iliac crest but distinct from the liver. She was frankly jaundiced. She had been jaundiced since the age of 4 weeks and the swelling of the abdomen had been noticed since the age of 3 weeks. A correct diagnosis of choledochal cyst was made by Dr. Richard Kieffer who, on July 21, 1950, performed a Roux-Y anastomosis between the cyst and the jejunum. At the time of operation 200 c.c. of bile was aspirated from the cyst, only partially emptying it. The child recovered uneventfully and up to the time she was last seen had had no further difficulty.* No attempts were made to outline the biliary tract either before or during the operation.

*Since this paper was submitted for publication, we have learned that S. H., Case 1, died of a ruptured appendix and peritonitis, 6½ years after operation; she had been well in the interim. The autopsy protocol, from the small hospital in which she died, is of great interest.

(footnote cont'd on following page)

A 3½-month-old female infant with jaundice since the third week of life and a huge choledochal cyst was successfully treated by Roux-en-Y anastomosis of the jejunum.

CASE 2.—M. T. (Mt. S. H.—47688), a 5-year-old girl, at almost monthly intervals from the age of 9 months had had severe attacks of pain and jaundice, occasional vomiting, and recently a palpable mass. Two years before, an appendectomy had been performed during an attack. When seen she was faintly jaundiced, no longer in pain, and had an easily palpable mass about 4 cm. in diameter in the right upper quadrant. Preoperative demonstration of the biliary tract was not attempted. At operation the cyst was found to lie largely behind the duodenum which was lifted directly forward. It was felt that a Roux-Y anastomosis would cause the duodenum to be obstructed by the jejunal loop which would necessarily lie across it and therefore a direct anastomosis was made between the duodenum and the underlying cyst, only one row of sutures being required for the posterior suture line.

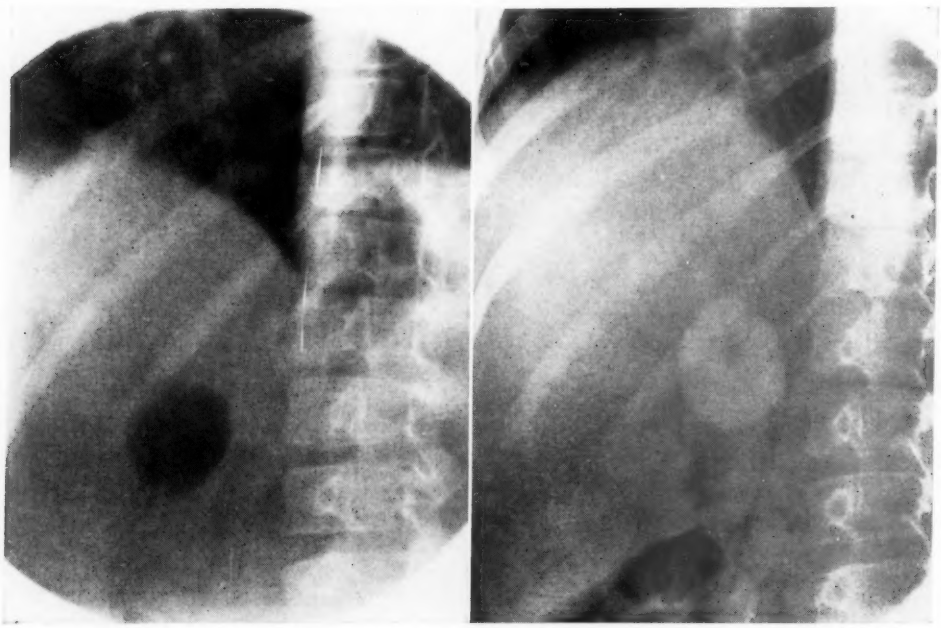


Fig. 1.—Case 2, M. T., a 5-year-old girl, with history of episodic attacks of abdominal pain, fever, and jaundice with easily palpable right upper quadrant mass, 4 cm. in diameter. At operation, July 19, 1955, a choledochal cyst was found lying almost completely retroduodenally. A cystoduodenostomy was performed. The child has been well since except for one or two mild attacks of pain in the 3 years since operation but without jaundice or palpable mass. *A*, Plain film of abdomen (July 2, 1957) 2 years after operation showing air in the cyst which is apparently little changed in size. *B*, Intravenous cholangiogram in left anterior oblique position (July 2, 1957) showing good concentration of contrast material in the cyst. A portion of the hepatic duct is visible proximal to the cyst.

The child has had one or two mild attacks of pain in the 3 years since operation but has never been jaundiced and has had no mass which could be felt. A plain film of the abdomen (July 2, 1957) 2 years after operation showed air in the cyst apparently little changed in size (Fig. 1, *A*). Intravenous cholangiography (Fig. 1, *B*) demonstrates the rounded sac which can also be seen to contain some air. The gall bladder is not demonstrated.

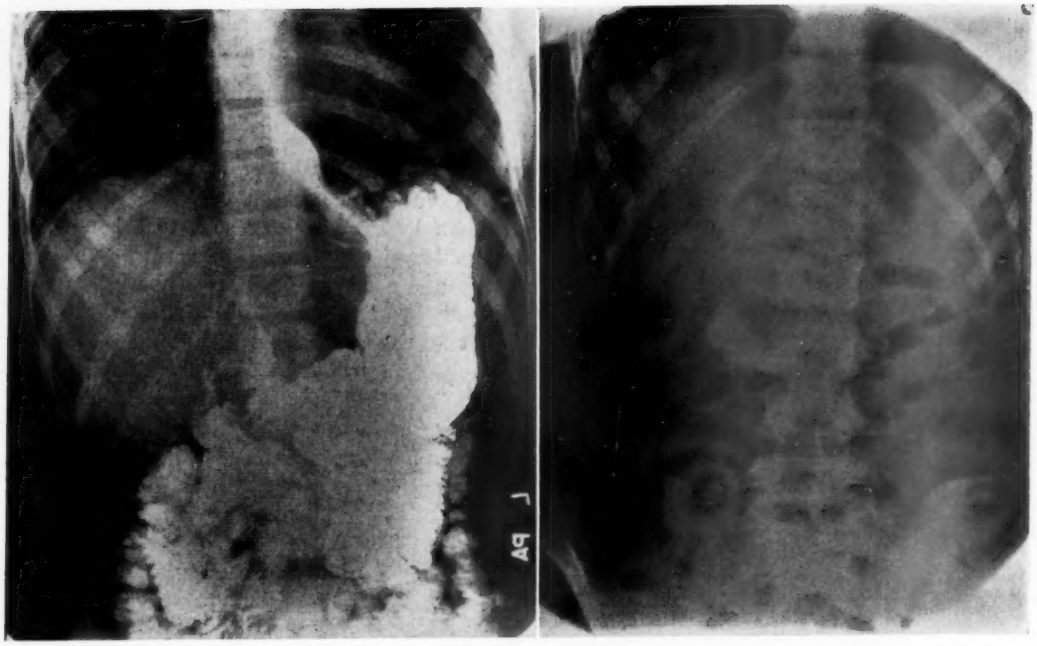
Cont'd from page 757.

The huge cyst found at operation 6½ years before was now greatly shrunken: "the upper portion of the common bile duct is markedly dilated, so that it admits the little finger and is anastomosed to a portion of small intestine in an end-to-end manner, no common bile duct can be palpated, nor can a [distal] opening from the anastomosed portion of bile duct be identified. . . ." A probe could not be passed into the ampulla of Vater and no distal common duct was found. Jaundice had been recognized in this baby at the age of 3 weeks. We must assume either that this was choledochal cyst in a child with atresia of the common duct or that the disused distal common duct had so shrunken as to escape detection at autopsy.

In a 5-year-old girl with episodes of pain, jaundice, and a palpable mass, the cyst, largely retroduodenal, was anastomosed to the duodenum with relief of symptoms.

CASE 3.—J. R. (J. H. H.—799255), a 13-year-old girl, for 4 to 5 years before admission to the hospital, had had repeated episodes of severe epigastric pain, thought to be colicky and requiring hypodermics for relief. The pain might last for as long as 2 to 3 hours and might come on at intervals of months to weeks. In March, 1957, she was reported to have had a severe bout of pain with a boardlike abdomen and a white blood cell count of 17,000. She was thought not to be jaundiced. Operation disclosed a normal appendix, which was removed, and considerable edema in the retroperitoneal tissues, especially about the mesentery of the transverse colon. She had a severe attack again 8 months later. On this occasion radiologic studies were performed. A gastrointestinal series (Fig. 2, *A*) showed a deformity of the duodenum. The cholecystograms (Fig. 2, *B*) revealed a well-filled small gall bladder with a cystic duct apparently leading to the upper end of the large cystic structure which was fairly well demonstrated by the contrast material. The diagnosis of choledochal cyst was made by Dr. Frank E. Brumback of Hagerstown, Maryland, by whom the patient was referred. There were no new findings on admission to The Johns Hopkins Hospital. We could not feel a mass, and there was no clinical or chemical evidence of jaundice. Intravenous cholangiogram before operation confirmed the findings of the oral cholecystogram (Fig. 2, *C*). Laminography at the time of the intravenous cholangiogram further substantiated the findings. A preoperative amylase determination was not made. Her cephalin flocculation was 3+ and her thymol turbidity was 2. On Feb. 21, 1958, the abdomen was entered through a subcostal incision, preparations having been made for operative cholangiography. We found at once an essentially normal gall bladder, and, behind and cephalad to the duodenum and occupying the space between it and the liver, a cyst perhaps 8 cm. in diameter, quite tense. A needle was inserted into the gall bladder and 10 c.c. of Hypaque (50 per cent) was injected into the gall bladder. This flowed easily without obstruction or resistance and the cholangiogram demonstrated what we had seen before in the preoperative cholangiograms, namely (Fig. 3, *A*), a small gall bladder connected by the cystic duct to the choledochal cyst which obviously was only partially filled. No other ducts were demonstrated at this stage. In the attempt to outline fully the cyst and its connections with the common duct, several further injections were made for serial roentgenograms (Fig. 3, *B*). With the last injection, reaching a total of 25 c.c., resistance to the injection was suddenly noticed and the gall bladder was seen to distend. As we stepped away from the operating table to allow the roentgenogram to be taken the anesthetist was queried as to whether the obvious pressure in the gall bladder was disturbing the patient. He remarked that the patient's blood pressure had fallen from 110 mm. Hg to 80. Within seconds the pressure had dropped to 70 and then to 50. The gall bladder was aspirated of 10 c.c. of thin green bile without any change in pressure. Twenty cubic centimeters of thin bile of similar character was then drawn directly from the cyst and almost immediately her pressure rose and, within 2 or 3 minutes, was back to normal levels. Her pulse had been slow throughout. Inspection of the pancreas now showed that whereas previously it had been quite normal, there was now a good deal of edema between the pancreatic capsule and the posterior parietal peritoneum. However, there was neither blood nor bile visible. The roentgenograms now showed a clearly outlined pancreatic duct which ended abruptly in its distal third and a very fine speckling of the entire pancreas suggesting a diffuse acinar filling (Fig. 3, *C*). The hepatic ducts seemed to join with the cystic duct, emptying into the cephalic end of the large choledochal cyst. The left hepatic duct was markedly dilated as had been demonstrated in the preoperative studies, the right one much less so if at all. A small portion of the common duct, normal in size, was seen to lead away from the lower end of the cyst toward the duodenum.

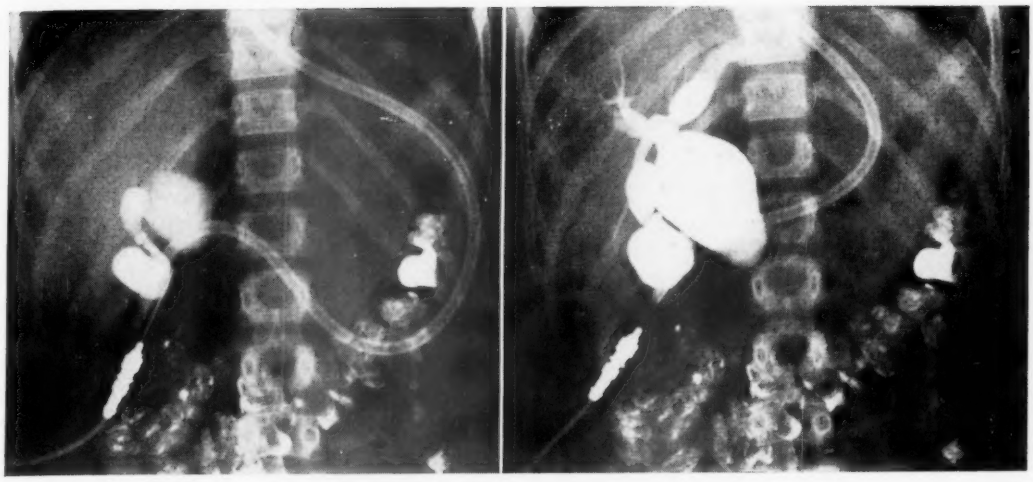
Fearing that we had probably produced an acute experimental pancreatitis, we rapidly performed an anastomosis between the cyst and the duodenum. A sump drain was placed down to the pancreas and put under constant suction in the attempt to withdraw any fluid which might accumulate. The patient's condition was excellent at all times thereafter and



A. *B.*

C.

Fig. 2.—Case 3, J. R., a 13-year-old girl, with history of 5 years of intermittent epigastric pain in severe attacks lasting several days reportedly without palpable mass or jaundice and a history of an appendectomy during one such attack with finding of edema of transverse mesocoln. *A*, Gastrointestinal series taken shortly after the appendectomy shows a deformity of the duodenal bulb by an extrinsic mass. The duodenum is displaced medially and in other views is seen to be displaced anteriorly. The characteristic crescentic defect in the second portion of the duodenum suggests the round contour of the cyst. (Courtesy of Dr. Frank E. Brumback, Hagerstown, Maryland.) *B*, Oral cholecystogram demonstrates a small well-filled gall bladder opposite the third lumbar vertebra. The cystic duct, which is rather large, can be seen to course cephalad and rather laterally, being displaced by a large round structure containing the contrast material and lying opposite the bodies of the first and second lumbar vertebrae. This is the choledochal cyst. (Courtesy of Dr. Frank E. Brumback, Hagerstown, Maryland.) The demonstration of a choledochal cyst by oral cholecystography is extremely unusual and has apparently been reported only twice previously. *C*, Intravenous cholangiogram (at 60 minutes). As compared with the oral cholecystogram the choledochal cyst here is seen somewhat more clearly and the gall bladder a little less clearly. A comparison with Fig. 3, *B* will show that the intravenous cholangiogram has demonstrated the left and right hepatic ducts as well as the substantial dilatation of the left hepatic duct. Demonstration of such cysts by intravenous cholangiography has apparently not been previously reported.



A. *B.*

C.

Fig. 3.—Case 3, J. R. At operation, there was found a tense cystic structure 8 cm. in diameter lifting the duodenum anteriorly and extending from below the second portion of the duodenum to the porta hepatis. The gall bladder was delicate, only partly filled, and not remarkable. *A*, Operative cholangiogram after injection of 10 c.c. of 50 per cent Hypaque solution into the gall bladder. The material flowed without resistance. The gall bladder, cystic duct, and choledochal cyst appear in the same relationship as in the oral and intravenous contrast studies undertaken before operation. The inlying duodenal catheter passes in front of the cyst even in its incompletely filled state. The barium in the colon is the residuum of studies undertaken before operation. *B*, An additional 10 c.c. of 50 per cent Hypaque was injected again without any resistance. Now, the gall bladder and cystic duct appear to be distended and the choledochal cyst is more completely filled reaching down to the third lumbar vertebra. The right and left hepatic ducts show up sharply and the left one, as suggested in the intravenous cholangiogram (Fig. 2, *C*), is of unusually large caliber. The common duct is not demonstrated. No contrast material has appeared in the duodenum. *C*, An additional 5 c.c. of 50 per cent Hypaque was injected into the gall bladder in order to demonstrate the common duct and the flow into the duodenum or any obstruction which might be present. The injection was discontinued when resistance was noted and the gall bladder was seen to be tense for the first time. While this film was being exposed the anesthetist reported a precipitous fall in the patient's pressure from 110 to 50 mm. Hg unaccompanied by any pulse rate change. Immediate aspiration of the gall bladder produced no change. The withdrawal of 20 c.c. of thin bile-colored fluid from the cyst resulted in immediate restoration of normal arterial pressure. It was noted now that the pancreas was surrounded by clear edema fluid uncolored by blood or bile. The cholangiogram demonstrates not only the short and undilated common duct ending abruptly in the region of the ampulla of Vater, but a large pancreatic duct which apparently empties into the choledochal cyst about the point at which the common duct takes origin. What is most disconcerting, of course, is the demonstration of the body and tail of the pancreas by a fine mistlike opaque shadow. This must represent contrast material either in the finest ductules or extravasated in the parenchyma. There is visible an abrupt change in caliber of the pancreatic duct midway in its course. A fulminating pancreatitis was anticipated. Serum amylase 30 minutes after operation was 1,260 mg. per cent reducing substance. For 3 days the patient complained of severe abdominal pain identical with that she had had in her earlier attacks. The serum amylase fell to 337 on the third day and to 266 on the fourth. Her course thereafter was uneventful.

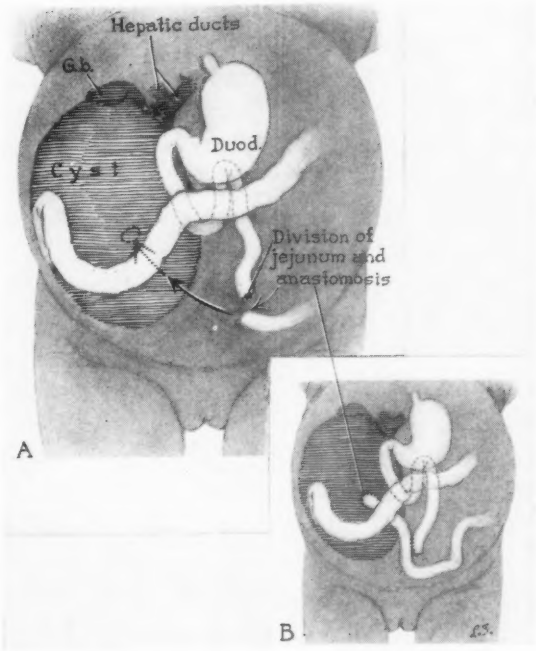
no fluid was obtained through this sump drain. It is of interest that for 2 or 3 days she had extremely severe epigastric pain which she said was exactly like that which she had had in her previous attacks. Her serum amylase taken immediately after operation was 1,260 and for about 6 hours she had a tachycardia of 120. On the next day her amylase was 1,039, then on the following day was 337, and on the fourth day 266. She had no further pain or difficulty. A gastrointestinal series taken 10 days after operation (Fig. 4) showed the barium to enter into the cyst.

Fig. 4.—Case 3, J. R., 10 days after operation. Orally ingested barium enters the choledochal cyst and passes into the right hepatic duct system. This is a common finding in patients with a direct anastomosis of such cysts to the duodenum, but appears to cause no difficulty. The patient has remained without symptoms in the 6 months since operation.

In a 13-year-old girl with repeated attacks of violent epigastric pain, the choledochal cyst was demonstrated preoperatively by both oral and intravenous cholangiography. At operation the cyst was demonstrated brilliantly by contrast material injected into the gall bladder. Continued injection demonstrated the hepatic and common ducts but also the pancreatic duct. The patient collapsed abruptly, responding to aspiration of fluid from the cyst. A cystoduodenostomy gave relief, but from the injection of contrast material the patient developed clinical pancreatitis in an attack simulating her preoperative attacks. Her subsequent course was smooth and she has remained well in the 5 months since operation.

DISCUSSION

The diagnosis of choledochal cyst can usually be made on the clinical grounds of recurrent pain and jaundice and a palpable abdominal mass and can occasionally be confirmed by preoperative radiographic studies. The diagnosis may be made with absolute precision at operation by the injection of contrast material into the gall bladder.



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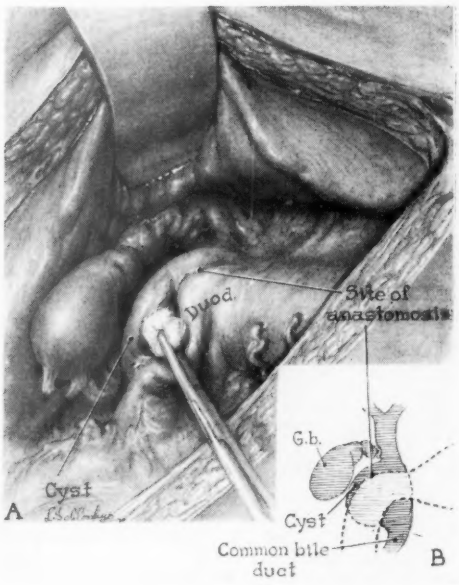

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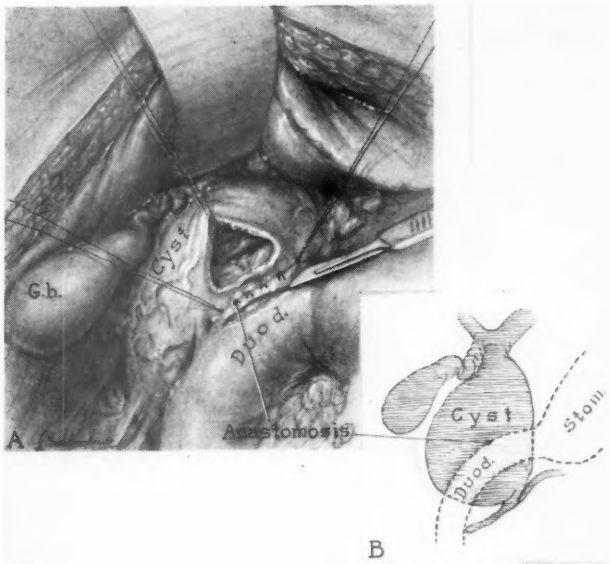

C.

Fig. 5.—*A*, Case 1. S. H., a 3½-month-old girl, with abdominal swelling since age of 3 weeks and jaundice since age of 4 weeks. The abdomen was greatly distended and symmetrically rounded by the large cyst. A Roux-en-Y anastomosis to the jejunum drained the cyst satisfactorily. *B*, Case 2. M. T., a 5-year-old girl, with history of attacks of pain, jaundice, and vomiting from the age of 9 months and recent appearance of a palpable mass. The cyst lay entirely behind the duodenum and the only feasible anastomotic procedure, a direct anastomosis of the adjacent structures, gave relief. *C*, Case 3, J. R., a 13-year-old girl, with history of repeated attacks of severe epigastric pain for 4 or 5 years. Jaundice had not been noted, nor a mass felt. The cyst extended from the liver to below the duodenum, which was lifted anteriorly upon it. It was feared that a Roux loop crossing the duodenum might obstruct it, so a direct anastomosis was performed between cyst and duodenum with satisfactory results.

Careful and precise delineation of the cyst and its communications will allow the precise decision as to the type of operative procedure to be performed and will reveal the occasional case in which the cyst is a large diverticulum off the main choledochus and can be excised. The almost instantaneous production of profound hypotension in our Patient 3, with injection of the cyst and filling of the pancreatic ducts with Diodrast under pressure, is of particular interest. The mechanism of such a sudden fall in arterial pressure so suddenly reversible by the relief in pressure in the cyst is of great interest and is under investigation. The patient unquestionably developed pancreatitis, demonstrated by the edema about the pancreas which developed almost immediately, by the striking elevation of the serum amylase, which gradually fell over the course of 4 days, and by the severe abdominal pain. It is of special interest that, in this child who had previously had numerous severe attacks of pain, the inadvertently produced regurgitation pancreatitis precisely duplicated her spontaneous attacks so far as she was concerned. Obviously, injections of contrast material into the cyst in these patients should be done under gravity with little or no pressure.

Most of the collected reports dealing with this anomaly indicate a substantial mortality in connection with operation for this condition, but many of these cases are from the older literature and, in others, attempts at extirpation or other improper operative procedures were performed.

The nature and cause of the anomaly remain uncertain. In most cases it consists of an aneurysmal dilatation of the common duct distal to the entrance of the cystic duct. A few reports suggest a primary obstructive mechanism. The facts that jaundice eventually supervenes, even though characteristically intermittent, and that dilatation of the hepatic ducts was seen in all 3 of our cases and was described in some reported cases indicate an obstructive element. This more likely may be the result of the presence of the cyst than the cause of it.

SUMMARY

Three cases of choledochal cyst or congenital cystic dilatation of the common bile duct are reported. Two were treated by anastomosis of cyst to duodenum in situ and one by a Roux-Y anastomosis of cyst and jejunum. All recovered without complications. Particular attention is directed toward the preoperative and operative radiologic investigation of these patients. The small, or largely retroduodenal, cyst should be treated by direct anastomosis between the duodenum and the cyst, and the larger cysts by a Roux-Y anastomosis to the jejunum. In one case acute pancreatitis was inadvertently produced by retrograde injection of contrast material under pressure and precisely duplicated the patient's preoperative attacks of pain.

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Calendar of Surgical Meetings

AMERICAN ACADEMY OF NEUROLOGICAL SURGERY. *Annual Meeting,* Nov. 5-8, 1958, Royal York Hotel, Toronto, Ontario, Canada. Secretary, Dr. Robert McLaurin, University of Cincinnati, Cincinnati, Ohio.

AMERICAN CANCER SOCIETY. *Annual Meeting,* Oct. 20-21, 1958, Biltmore Hotel, New York City, N. Y. Secretary, Dr. Scott Hill. Subject, cancer of the colon and rectum.

AMERICAN COLLEGE OF SURGEONS. *Clinical Congress,* Oct. 6-10, 1958, The Conrad Hilton, Chicago, Ill. Secretary, Dr. Michael L. Mason, 40 E. Erie St., Chicago, Ill.

AMERICAN MEDICAL ASSOCIATION. *Annual Meeting,* Dec. 2-5, 1958, Leamington Hotel, Minneapolis, Minn. Deadline for submission of abstracts, Aug. 1, 1958. Secretary, Council on Scientific Assembly, Dr. Thomas G. Hull, 535 North Dearborn St., Chicago 10, Ill.

SOCIETY OF UNIVERSITY SURGEONS. *Annual Meeting,* Feb. 12-14, 1959, Denver, Colo. Secretary, Dr. James D. Hardy, University of Mississippi Medical Center, Jackson, Miss.

SOUTHERN SURGICAL ASSOCIATION. *Annual Meeting,* Dec. 9-11, 1958, Boca Raton Hotel and Club, Boca Raton, Fla. Attendance by invitation of membership only. Secretary, Dr. George G. Finney, 2947 St. Paul St., Baltimore 18, Md.

SOUTHERN THORACIC SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 28-30, 1958, Deauville Hotel, Miami Beach, Fla. Secretary, Hawley H. Seiler, M.D., 517 Bayshore Blvd., Tampa 6, Fla.

WESTERN SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 20-22, 1958, Hotel Kahler, Rochester, Minn. Deadline for submission of papers, Sept. 1, 1958. Secretary, John T. Reynolds, M.D., 612 N. Michigan Ave., Chicago 11, Ill.

Appraisal of Progress in Surgical Therapy

CONDUCTED BY WARREN H. COLE, M.D.

INDICATIONS FOR HEMIPELVECTOMY

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INTRODUCTION

IN THE period from Nov. 11, 1946, to Feb. 10, 1958, we have performed 43 hemipelvectomies for tumors of bone. Several other authors have published sizable series of cases for bone tumors as well as other conditions (not always malignant) so that we may well evaluate the indications and contraindications for this radical procedure. The technical details of the operation and the preoperative and postoperative care have been reported previously.[1, 2] They will not be repeated here.

We have had 3 postoperative deaths in our series which represents a mortality rate of 7 per cent. Two of these followed hypotensive anesthesia (which we have since abandoned) within 6 hours in one case and within 36 hours in the other. Autopsy in both instances revealed no residual tumor and both deaths were attributed to hemorrhage, shock, and hemaglobinuric nephrosis. The third death occurred 6 hours after operation in a 48-year-old woman who appeared to present a favorable situation of a secondary chondrosarcoma in the upper right femur with recurrence after local excision and extension into the acetabulum. Preoperative chest x-ray was negative for pulmonary metastases. Autopsy revealed residual tumor in the region of the lumbar vertebrae and metastases to the heart and jejunum.

In the earlier years following the first successful hemipelvectomy by Girard in 1895, a very formidable mortality rate ranging between 50 and 75 per cent was a serious deterrent to a decision to perform this operation. However, in the past 15 years, largely due to modern methods of dealing with shock, infection, hemorrhage, and anesthetic complications, a favorable mortality rate comparable to ours removes one major objection to acceptance of this mutilating procedure.

DEFINITION

The term "hemipelvectomy" as we use it is defined as a one-stage resection of the hindquarter which incorporates the lower extremity and the hemipelvis including the entire innominate bone from the symphysis pubis

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anteriorly to the sacroiliac joint posteriorly (Fig. 1). Any procedure which does not divide through the sacroiliac joint and the symphysis pubis should not be classified as a hemipelvectomy.

Hindquarter amputation is a satisfactory descriptive alternative term and other synonyms include the terms disarticulation of the innominate bone, interpelviabdominal amputation, transiliac amputation, and sacroiliac disarticulation.

Fig. 1.—The right innominate bone has been completely removed from the sacroiliac joint to the symphysis pubis. A portion of the first 3 sacral segments has been removed because the tumor extended to the sacroiliac joint. There was local recurrence one year later in the margin of the sacrum.

TECHNICAL CONSIDERATIONS

While hemipelvectomy has been done for a variety of conditions we are primarily concerned here with the indications in the field of bone tumors. The benign bone tumors are amenable to conventional conservative measures, but it is conceivable that a giant-cell tumor, a fibrous dysplasia, or a chondroma may be so extensive or so situated that this radical amputation would be justifiable to eradicate the disease completely or to obviate malignant transformation particularly if previous conservative attempts had met with failure. If we suspect, or know, that early malignant change has already supervened we are all the more influenced in a decision to proceed with a hemipelvectomy (Figs. 2 and 3).

The extent of the disease will largely determine the decision as to operability. Tumors of the upper femur may be so close to the hip joint or so bulky that a hip joint disarticulation would not completely eradicate the disease (Fig. 4). Then hemipelvectomy is a proper procedure. Seven cases in

our series belong in this category. In 3 cases in our series hip joint disarticulation had been carried out for femur lesions followed by recurrence in the acetabulum (Fig. 5) necessitating hemipelvectomy. One of these patients died of metastasis 2½ years later. The other 2 are alive and well 3 years and 6½ years, respectively, after operation.

Fig. 2.

Fig. 3.

Fig. 2.—A benign giant-cell tumor of the upper left femur had been treated by curettage and bone graft. It recurred 2½ years later and spread to the acetabulum. Malignant transformation was suspected and the final pathologic report revealed malignant giant-cell tumor. Patient is alive and well 3 years after operation.

Fig. 3.—Specimen shows extent of malignant giant-cell tumor of the femur invading the iliac bone.

A large tumor may project posteriorly or laterally from the iliac crest. Or the growth may arise in the superior ramus of the pubis (Fig. 6) and project into the pelvis or outward. In these circumstances the size of the tumor is not a deterring factor but the critical feature is the proximity of disease to the joint line. If tumor extends to, or across, either the sacroiliac joint or the symphysis pubis, operability is out of the question. We attempted one case in which there was x-ray evidence of sacroiliac joint involvement and excised the lateral portion of the first 3 sacral segments along with the hemipelvectomy specimen (Fig. 1). Inoperable recurrence in the sacrum was manifested a year later.

Fig. 4.—Extensive chondrosarcoma involving the upper shaft and neck of the right femur. Hip joint disarticulation obviously would not encompass the entire tumor. Patient is alive and well 15 months postoperatively.

Fig. 5.—Biopsy established a diagnosis of chondrosarcoma in the upper right femur. Hip joint disarticulation was done, but recurrence in the stump was demonstrable 20 months later. Patient is alive and well 6½ years since hemipelvectomy.

Another patient who had multiple osteochondromata (Ollier's disease) presented malignant change in one such lesion in the left superior pubic ramus. At operation this was found to extend well within the pelvis and to cross the midline. Within 2 years after hemipelvectomy, recurrence anteriorly was detected and, although 2 attempts were made surgically to remove the recurrences, they were inoperable and x-ray therapy was finally resorted to for its palliative effect.

Fig. 6.—Mixed type of osteogenic sarcoma of the superior ramus of the left pubis extending medially to the symphysis pubis. Patient died of pulmonary metastases 3 months later despite the fact that the preoperative chest roentgenogram was clear.

Tumors arising in the acetabular area usually present no technical problems. If any of the soft pelvic structures are involved by proximity of the primary tumor or invasion, serious thought must be given to the feasibility of a hemipelvectomy. In limited circumstances the operation may be undertaken with impunity. The first stage of the operation may be undertaken to the step where the intrapelvic involvement can be determined by direct vision and palpation and operability determined before one reaches that "point of no return" which is ligation and division of the external iliac artery and vein. We have one case in our series in which it was necessary to excise a portion of the lateral wall of the vagina that was densely adherent to an ischial malignant giant-cell tumor. That patient is alive and well 6 years later. In another patient the tumor completely surrounded the rectum, necessitating resection of the lower half of the rectum with the specimen. The patient died 13 months later of pulmonary metastasis.

Considerable thought must be given to the patient who has had previous treatment such as biopsy, partial excision, or irradiation. Postoperative scar tissue or irradiation fibrosis will add considerably to the difficulty of dissection since cleavage planes are lost or obliterated, but by proceeding with caution this difficulty usually can be overcome.

It is our considered opinion that just because the operation is technically feasible is not alone sufficient justification for the procedure. Other factors must be taken into consideration in reaching a decision. The objective should be a reasonable chance of cure or, at least, the likelihood of a reasonable period of comfortable convalescence. If pain relief is the principal problem, cordotomy may be just as efficacious.

CLINICAL CONSIDERATIONS

The major factor in determining suitability is an exact diagnosis. Consider the 5 main groups of malignant bone cancer: (1) osteogenic sarcoma, (2) Ewing's endothelioma, (3) primary reticulum-cell sarcoma of bone, (4) multiple myeloma, and (5) metastatic cancer to bone. Of these, only the first, osteogenic sarcoma, merits our serious consideration. Both Ewing's endothelioma and primary reticulum-cell sarcoma are radiosensitive tumors and we believe that they should be treated by irradiation methods with adjuvant chemotherapy. True enough we may be required to amputate an extremity later for failure of radiation therapy or complications such as pathologic fracture or radionecrosis, but at this late stage an amputation is not broached with any conviction of obtaining a cure. It is usually a palliative recourse and we do not regard with enthusiasm the futile gesture of a palliative hemipelvectomy.

By its very name, plasma-cell myeloma connotes a multicentric or polyostotic tumor. Even if the earliest skeletal survey indicates a solitary lesion, we may rest assured that other stigmas of the disease sooner or later will reveal themselves in the bony skeleton. Removal of any disease by hemipelvectomy would certainly not be curative and therefore the operation would seem unjustified. Until it can be conclusively demonstrated that early excision, such as by rib resection, of a so-called solitary plasmacytoma may be followed by long-range control, we do not favor hemipelvectomy in plasma-cell myeloma.

In metastatic cancer the very nature of the disease having demonstrated its propensity to spread to other parts of the body offers little or no prospect that removal by hemipelvectomy of a presently single metastasis will cure the patient even if the primary lesion also is or has been removed. Even if both foci are removed, it is our conviction that the primary tumor has "sown its seeds," one of which has been detected with others due to manifest themselves sooner or later. Until other methods of treatment evolve, it remains a sad fact that once a cancer has metastasized that patient will succumb to metastatic cancer even though long-range worthwhile palliation may be obtained in some cases by more conservative approaches to the individual problem.

It is true that palliative amputation may occasionally be indicated in certain selected cases of metastatic cancer. We have one patient with treated cancer of the cervix and a metastasis to the tibia which failed to respond to radiation therapy. A low thigh amputation was performed 6 years ago and

this patient is currently free of disease. But we would regard a hemipelvectomy, if theoretically indicated, as a pretty drastic equivocal attempt at relief in practically any case of metastatic cancer.

There remains for consideration the group of bone sarcomas classified under the general term of "osteogenic sarcoma." In this over-all designation we recognize 3 different types: (1) chondrosarcoma, (2) fibrosarcoma, and (3) osteosarcoma.

Osteosarcoma is the condition frequently inferred by the broader term "osteogenic sarcoma." It is a highly malignant sarcoma usually lytic in nature but sometimes laying down much osteoid giving a dense or sclerosing configuration to the roentgenogram. They all tend to metastasize early to the lungs and the 5-year survival rate is only approximately 10 per cent of determinate cases. When early amputation in this class of lesion yields such poor results, hemipelvectomy hardly seems justified when the patient is prone to succumb to pulmonary metastases before the surgical wound is completely healed.

Fibrosarcoma may be medullary or periosteal and, since their behavior is unpredictable, more serious consideration may be given to cases presenting this type of biopsy diagnosis. We would include the malignant giant-cell tumors in this category. In general the 5-year survival rate in this class is somewhat better than for osteosarcoma so a favorable decision is more readily reached, particularly if the lesion is early, in a favorable location, and has not been subjected to extensive prior treatment. We have 7 cases in this category with 4 alive and well 18 months, 3 years, 4 years, and 6 years, respectively, since operation. One patient died of carcinoma of the rectum one year posthemipelvectomy and autopsy revealed no residual disease or metastases of the osteogenic fibrosarcoma. The other 2 patients died 2½ months and 6 months, respectively, postoperatively from pulmonary metastases despite the fact that preoperative chest films were interpreted as clear.

A chondrosarcoma of high degree of malignancy is apt to behave like the osteosarcoma type and therefore is ill suited for hemipelvectomy. The prime condition for which hemipelvectomy is most suited is the group of tumors that are categorized by the pathologist as chondrosarcoma particularly if further grading as to degree of malignancy is possible and the tumor is pronounced low-grade or moderate. Many of these are secondary in nature and represent a malignant transformation in a long pre-existing benign enchondroma or osteochondroma. It is in this group that critical judgment may be required in diagnosis, for often biopsy reveals only benign chondroma whereas the clinical setting and the roentgenograms favor a diagnosis of a malignant tumor. Frequently the onset of the malignant change is heralded by the subjective complaint of pain, either deep bone pain where none previously existed or a change in the nature and type of pain that had been produced by the pre-existing benign tumor. In this situation clinical judgment must prevail. In 2 instances we have done a hemipelvectomy in the face of a benign pathologic report on biopsy only to have the correctness of our clinical opinion confirmed by subsequent developments.

GENERAL CONSIDERATIONS

The first proviso, then, in determining operability is microscopic confirmation of the diagnosis with added attention given to the type of osteogenic sarcoma—whether osteosarcoma, fibrosarcoma, or chondrosarcoma. In the great majority of cases this is readily accomplished by aspiration biopsy of a representative area of the presenting tumor. If this is unsuccessful, open surgical biopsy may be employed with due attention to the recommended principles of closure of the biopsy wound without drains and without packing to insure primary wound healing. The only problem that may arise occurs when the microscopic sections on aspiration or open biopsy reveal *benign* chondroma. Then surgical judgment based upon roentgenographic interpretation and clinical assay must prevail, for even though the histologic features may be benign the clinical behavior of some of these cartilaginous tumors may be malignant and a radical approach is justified.

Since malignant bone tumors tend to metastasize to the lungs, the next step is to check the pulmonary fields clinically and roentgenologically. The demonstration of one or more metastatic deposits in the lungs should be sufficient cause to forego the amputation. There may occur the rare case with a solitary metastatic deposit in the periphery of the lung which is amenable to removal by wedge resection or lobectomy, in which event critical evaluation may favor proceeding with hemipelvectomy for reasons of possible relatively long-rang palliation or, perchance, even cure.

Attention should next be directed toward the local disease. The size of the growth and conditions imposed by previous therapeutic attempts must be considered. Tumors in the upper femur which can be completely eradicated by hip joint disarticulation need not be subjected to hemipelvectomy just to be theoretically doubly certain. If the tumor in the innominate bone crosses either joint to invade the sacrum posteriorly or the contralateral pubis anteriorly it is extremely doubtful that hemipelvectomy can be done without almost certain local inoperable recurrence.

Much information can be gained by abdominal palpation and digital rectal and vaginal examination to determine the degree that the tumor extends within the true or false pelvis. Barium enema and intravenous pyelogram will materially aid in determining displacement of bowel or bladder by tumor. Then speculum visualization, cystoscopic, and proctoscopic examination may be done to insure that the vaginal, bladder, and rectal mucosal surfaces are not involved. Some authors recommend exploratory laparotomy to determine operability, but it is our belief that as much can be learned preoperatively by the maneuvers described and that a preliminary additional major operation is seldom necessary and therefore is better avoided.

The general condition of the patient must be given consideration and any deficiencies disclosed by routine urinalysis, hemogram, and general physical examination suitably corrected. The physiologic age of the patient is of more significance than the chronologic age. Seven of the patients in our series were over 60 years of age when operated upon and their convalescent course paralleled that of the younger age group.

As a final criterion it is essential to have the patient's wholehearted consent for this operation. Naturally this will not be spontaneous but the excess time devoted to this aspect by the surgeon preoperatively will be well repaid in the smoother physical and psychologic recovery. The full extent of the procedure should be painstakingly outlined to the patient and the greatest incentive is a visit or two from a patient who has had a hemipelvectomy, particularly if he is wearing a satisfactory prosthesis.

RESULTS

A statistical analysis of the results in our series of 43 cases is shown in Tables I, II, and III.

TABLE I. OVER-ALL RESULTS TO FEB. 10, 1958

Failures	
Died of disease	19
Operative deaths	3
Alive with metastases	5
	27
Alive and free of disease	16
	43

TABLE II. FIVE-YEAR RESULTS IN ALL CASES (Nov. 11, 1946, to March 26, 1953)

Died of disease	17
Alive with metastases	1
Alive and free of disease	8
Total	26
5-year survival rate	30.7%

TABLE III. FIVE-YEAR RESULTS IN CHONDROSARCOMA GROUP (Nov. 11, 1946, to March 26, 1953)

Died of disease	12
Alive with metastases	1
Alive and free of disease	7
Total	20
5-year survival rate	35%

Of our 43 cases, 27 were considered failures: 19 died of disease, 3 were operative deaths, and 5 are alive with metastases. Sixteen are alive and free of disease. Five-year follow-up of all cases from Nov. 11, 1946, to March 26, 1953, showed a survival rate of 30.7 per cent. There were 26 patients in this group. Of these, 17 died of disease, one was alive with metastases, and 8 were alive and free of disease. The 5-year survival rate from Nov. 11, 1946, to March 26, 1953, for the chondrosarcoma group of 20 patients was 35 per cent. Twelve of these patients died of disease, one was alive with metastases, and 7 were alive and free of disease.

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Editorial

CONDUCTED BY I. S. RAVDIN, M.D.

The Pyloric Antrum—The Relative Extent of Distal Gastrectomy Necessary to Insure Its Complete Extirpation

In various medical centers throughout the country, the operation of bilateral subdiaphragmatic vagotomy combined with antral extirpation, or so-called hemigastrectomy, for the surgical treatment of duodenal ulcer is being accepted with increasing favor. Cases have been observed for over a decade and results to date suggest that the incidence of recurrent ulceration seems to compare quite favorably with those cases subjected to an adequate subtotal gastric resection. The procedure appears to be a physiologic surgical approach to the problem, being directed at eliminating the two main sources responsible for gastric hypersecretion in the patient with duodenal ulcer. The importance of the vagal pathway as a mediating factor in gastric hypersecretion occurring during the fasting state has been well documented by the monumental work of Dragstedt. Likewise, Edkins, Dragstedt, Harkins, and their co-workers have demonstrated the importance of the gastric antral mucosa as the sole source of the hormone *gastrin*, which in turn is responsible for initiating a hypersecretion of the fundic glands. Sauvage, from work with his ingenious pouch preparations, feels strongly that the hypersecretion of antral origin is more important in the perpetuation of ulcer disease than is hypersecretion via the vagus nerves.

The abdominal surgical approach to the vagus nerves is now a well-standardized procedure. The clinical end results, however, depend largely upon the completeness in which the nerve division is carried out. A thorough search must always be made for accessory nerve fibers; a lysis of all fibrous and areolar tissue in the subdiaphragmatic periesophageal compartment must also be performed.

When one turns his attention to the pyloric antral extirpation, or so-called hemigastric resection, the following questions are frequently asked: (1) What constitutes the antral segment, and are there any precise anatomic landmarks on the lesser and greater curvatures of the stomach which serve as a guide to the surgeon in determining the proximal limit of the resection? (2) How much of the distal stomach is actually removed in order to completely excise the gastric antrum?

Most standard textbooks depict the pyloric end of the stomach and antral segment as comprising only about 15 to 20 per cent of the distal part of the stomach. Some texts state that the antrum extends along the lesser curvature

to the incisura angularis and along the greater curvature to a variable and inconstant point opposite the augularis. It must be remembered, however, that the angularis represents an inconstant landmark and its location on the lesser curvature varies with peristaltic activity, the relative amount of gas in the stomach, and with changes in the patient's posture. Some surgeons employ a point on the lesser curvature at the junction of the first and second coronary veins as representing the upper or proximal anatomic extent of the antral segment. However, again, the coronary veins are variable in their location and all too frequently are obscured in the individual with a large infiltrate of fatty tissue in the gastrohepatic omentum.

Erik Landboe-Christensen, of Copenhagen, in studying 47 human stomach specimens removed from patients of different age groups, was able to demonstrate a sharp macroscopic transition between the pyloric and fundic gland areas in the majority of cases by employing a water-acetic acid clearing technique. His conclusions were that the pyloric antral zone occupied a greater length on the lesser than on the greater curvature. His measurements and calculations depicting the extent of the antral segment demonstrated that this portion of the stomach occupied approximately 44 per cent of the length of the lesser curvature and approximately one-eighth, or 12 per cent, of the distal extent of the greater curvature.

In regard to the clinical application of the problem, in relation to complete surgical excision of the gastric antrum, at operation one first estimates the distance on the lesser curvature from the pyloric vein to the gastroesophageal junction. A site is then selected for division of the stomach just proximal to a point midway between the latter two structures. This site of division is usually located 2 to 4 cm. proximal to the incisura angularis. A similar midway point on the greater curvature is selected for bisection of the stomach. Two straight Kocher clamps are placed at right angles to the long axis of the stomach along the greater curvature at the point selected. This portion of the stomach is then divided. Clamps are placed from this point of division in an oblique manner to the lesser curvature up to the point selected for division. This section of the stomach is transected. The relative extent of the gastrectomy possibly represents about a 40 per cent resection in terms of total mucosal surface area. The resection, no doubt, removes slightly more than the antral segment, but it should be stressed that the proximal extent of the antral glands does not terminate in an abrupt transition, but gradually blends with the distal glands of the fundus. A resection including slightly more than the antral segment merely insures the operator of a complete antral extirpation, but the extent of the gastrectomy does not unduly sacrifice the function of the stomach as a storage organ.

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Surgical History

CONDUCTED BY JOHN R. PAINE, M.D.

JOSEPH FRANÇOIS MALGAIGNE AND MALGAIGNE'S FRACTURE

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Securité *Simplicité* *Celerité*

SOME surgeons are remembered as great technicians; others as great teachers. Medical folklore is full of tales of surgeons remembered because of, or in spite of, their eccentricities. It is an unusual surgeon, however, whose name lives on because of his literary genius as an author and editor. Joseph François Malgaigne was such a man. An experienced surgeon, he was actively engaged in the practice of his profession throughout his life. A scholar, he searched out original sources for their meaning without relying upon translators and compilers. A gifted teacher, he was accustomed to marshalling minutiae into concise and logical patterns. Blessed with these talents, he used them efficiently, with the result that the surgical literature of his time was enriched.

The *Traité des fractures et des luxations*[5] appeared in 1847. This is a comprehensive two volume work with a sumptuous supplementary atlas of plates. The first, and smaller, volume deals with fractures; the second, and larger, volume deals with dislocations. It is the finest and most complete work on fractures to be published up to that time, far exceeding Astley Cooper's *Treatise on Dislocations and Fractures of the Joints,* both in scope and execution.

"The character which I have mainly sought to give this work is that of reality. In a historical point of view, I have aimed at presenting a resumé of all the doctrines and ideas maintained from the earliest times to our own day, having recourse as much as possible to the original works. As to my teachings, I have asserted nothing unsupported by facts, drawn either from my own experience or from that of others. Where clinical observation was insufficient, I have sought a substitute for it in experiments upon dead bodies, or upon the lower animals; but above all, I have tried to clear up a great many mooted points by throwing upon them the light of pathological anatomy; and this is the object of my atlas."[5]

The opening statical analysis of 2,328 patients with fractures seen at the Hotel Dieu over an 11-year period is unique for this period. The patients are classified according to age and sex, the time of year the fracture occurred, and

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the bone fractured. It is interesting to note that only 30 of the 2,328 patients were found to have more than one fracture, an indication that the forces producing injuries one hundred years ago were of a lesser magnitude than those encountered today when multiple fractures are frequent.

The principles upon which Malgaigne's treatment of fractures and dislocations are based are those handed down through Paré, Petit, Desault, Boyer, and Dupuytren, in a great tradition of French surgery. Malgaigne, however, was not afraid to break with this tradition when his own observations and experiences showed the old masters to be in error. He advocated the use of the semiflexed position in reducing fractures of the lower extremities as described by Pott, in opposition to the methods of Desault, Larrey, Bichat, Cloquet, and others. He proved his point by a series of ingenious experiments upon animals and cadavers, in which he showed that when the quadriceps and hamstring tendons are cut simultaneously with the knee partially flexed, the tendons retract equal distances, demonstrating that in this position the opposing muscles are equally balanced. Such is not the case when the tendons are sectioned with the knee fully extended.

Little escaped his observing eye or his inquiring mind. He describes a patient with an ischemic contracture of the forearm due to a dressing too tightly applied, 34 years before Volkmann. He was led to investigate the gas produced during gas gangrene infection, managed to collect a quantity, found that it burned with a blue flame, and identified it as carburetted hydrogen. He was imaginative in his approach to technical problems such as maintaining the fragments of a displaced transverse fracture of the patella in apposition. For this, he devised an apparatus with which two sets of hooks could be inserted subcutaneously into the fragments and, drawn together by a threaded screw, approximate the fragments; these are Malgaigne's hooks.

Malgaigne's Fracture (Double Vertical Fracture of the Pelvis).—"Under this name I shall describe a form of multiple fracture of the pelvis, distinguished from all others by a species of regularity, and meriting, besides, special attention in the triple aspect of diagnosis, prognosis, and treatment. It is a combination of two vertical fractures, separating at one side of the pelvis a middle fragment comprising the hip joint; according as this fragment is carried upward or inward, the femur follows its movements, and hence result changes in the length and direction of the limb which have often misled practitioners.

"Of these two fractures, the anterior is almost constantly seated in the horizontal and descending rami of the pubes, separating this bone from the ilium and iscium; the posterior is always back of the cotyloid cavity, and generally in the ilium; once, however, it was seen by Richerand in the sacrum. Lastly, instead of a fracture, we may have here a separation of the sacro-iliac symphysis; of which an instance is reported by M. Gerdy."

"The diagnosis is quite easy when we can readily feel the middle fragment moving under our finger;—the diagnosis is completely made out by seeking the signs of the anterior fracture in the perineum and fold of the groin; and those

of the posterior fracture back of the trochanter, while the existence of any of the displacements alluded to may be detected by the finger introduced into the vagina or rectum. The prognosis is rendered serious mainly by the injury inflicted on the viscera.''

In the magnificent atlas volume accompanying his work on fractures and dislocations, Malgaigne shows a specimen taken from the Musée Dupuytren which shows a bilateral anterior subluxation of the sacrum with a fracture of the pelvic ring anteriorly (Fig. 1). The specimen was taken from a 48-year-old man who died 5 days after being run over by a carriage. This case was fully reported by Foucher. The more frequent type of Malgaigne's fracture consists of the fractures of the hemipelvis, through the pubic rami in front and the ilium behind, with displacement of the lateral fragment upward.

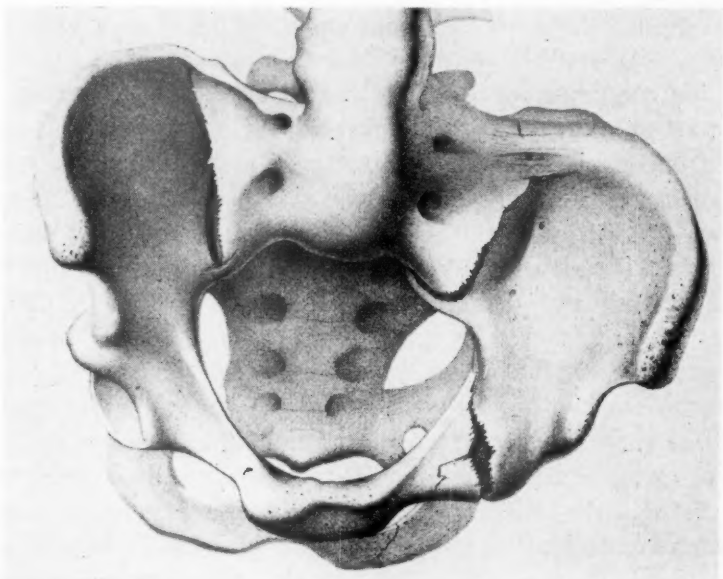

Fig. 1.—A rare example of Malgaigne's fracture taken from the atlas volume of his work on fractures and dislocations.

Malgaigne emphasized the importance of accurate diagnosis since the physical signs, such as shortening and displacement of the greater trochanter upward, could easily suggest a fracture of the hip. In restoring the normal relationship of the fragments by manipulation and traction, he pointed out that the usual method of applying traction to the limb, that of Desault, depended upon counter traction against the ischial tuberosity and therefore would not be effective in such a case.

Joseph François Malgaigne was born, Feb. 14, 1806, at Charmes, in the valley of the Moselle, where his father, an old army surgeon, was the local health officer. At first he attended public school, but later he was able to go to a private school where one of his teachers, François Alliott, aroused his interest in Latin and Greek. As a result of the stimulus of this exceptional teacher, Malgaigne was early provided with the tools he needed for historical

investigation. At what to us may seem the tender age of 15 he was sent to Nancy to begin his medical education. His letters to his father have been preserved and provide an interesting picture of his life during this period.[8] At 19, he was qualified as an *officer de sante,* or health officer.

During his medical studies, Malgaigne found, or took, the time to try his hand as a writer. His initial effort, a historical tragedy, *La conspiration des Espagnols contre Venise,* received one performance by amateur actors. A comedy, *Les caprices,* followed its predecessor into oblivion without even one performance. In 1825, collaborating with a journalist in Nancy, he published a magazine, *Propagateur de Lorraine,* which was promptly suppressed by government agents because of its "liberal color," this being the period of Bourbon counterrevolution.

With his medical education temporarily at an end and his literary career abruptly extinguished, he was at loose ends. When he was offered a position as secretary to M. de Villeneuve, a historian, he accepted. In this capacity he renewed his acquaintance with Latin and Greek and observed the methods and techniques of a historian. During this brief interim, the decision to go to Paris for further medical training was made.

The decision to go to Paris was opposed by his family who felt that he was old enough to settle down. After all, his father had been satisfied to be an *officer de sante.* As a result of this conflict, Malgaigne left for Paris without the support of his family and almost completely without funds. His early years in Paris were marred by hardship and occasionally by real privation. Nevertheless, he worked hard and with success; he received a prize in 1827 for a paper, *Nouvelle theorie de la Voix humaine.*

About this time, in an effort to improve his financial condition, he entered the regular army as a medical officer. His first commanding officer, Pierre Gama, had had a distinguished military career during the Napoleonic wars. In times of peace he was a student of military history and the history of military medicine. He and Malgaigne became fast friends. Years later Gama was a witness at Malgaigne's wedding. After an encouraging beginning, promotion, praise, and promise of future opportunities, Malgaigne became dissatisfied. His transfer to the field from hospital service provided the pretext for his resignation.

The revolution of 1830 in Paris must have been congenial to his republican spirit. One wonders if he assisted Dupuytren at the Hotel Dieu during those "glorious July days." Dupuytren could have used his help for the Hotel Dieu was filled with wounded from either side.

In the fall of 1830 the Poles revolted from their Russian masters and appealed to the new French government for help. Malgaigne organized a volunteer hospital unit, consisting of 9 surgeons and other personnel, and led it in action in support of the Polish army. He distinguished himself under fire during several engagements. With the collapse of the revolution, the inevitable epidemic of cholera appeared. Malgaigne returned to France decorated, disillusioned, and with a physical abhorrence to cold which lasted the rest of his life.

After these interruptions, Malgaigne finally received his degree as a doctor of medicine.

Characteristically, Malgaigne published an account of his experiences in Poland which was widely circulated. This came to the attention of Jules Guerin, one of the most controversial figures among the surgeons of Paris and a pioneer in the treatment of orthopedic conditions. Guerin had established his own hospital for the treatment of the crippled and deformed at Passy near the residence formerly occupied by Benjamin Franklin. He believed that scoliosis was caused by, or made worse by, muscle contractures and advocated treating such cases by means of multiple subcutaneous myotomies. Valentine Mott was much taken by Guerin, and enthusiastically describes an operation in which more than 50 muscles were sectioned in order to correct deformity. Guerin was the editor of the *Gazette medicale de Paris*, a weekly magazine with a circulation of 1,500, the most popular and the best French medical journal of its day. Malgaigne was invited to become an associate editor, a position he held for several years.

Malgaigne gained valuable experience while working with Guerin on the Gazette, as well as having an opportunity to develop his claws as a reviewer: "The work of M. X contains many things both new and good. Unfortunately the good things are not new, and the new things are not good." This was to stand him in good stead when in 1840 he founded the *Journal de chirurgie*, and in 1847 when he became chief editor of the *Revue medico-chirurgical de Paris*.

It is as an editor that Malgaigne exerted his greatest influence upon his contemporaries. He was a staunch advocate of the statistical approach to the study of medical problems and encouraged animal experimentation. Young men and new ideas always gained a hearing on the pages of his journals.

The medical journals of Paris at this time were a far cry from the staid journals of today. Controversy and invective, "yellow journalism," was commonplace. Such an exchange between the former associates, Guerin and Malgaigne, led to a famous lawsuit in 1843 when Guerin sued for defamation of character. The basic point at issue was an important one. Can the results of clinical investigations and laboratory experiments which demonstrate the ineffectiveness of methods of treatment strongly advocated by various individuals be published with impunity? In the uproar created by the suit, among the physicians Malgaigne had the greatest popular support as an advocate of freedom of inquiry and freedom to publish opinions based on investigations. After a long public trial in which Malgaigne gave an impassioned speech in his own defense, the case against him was dismissed.

In his role as a medical editor, Malgaigne kept in close touch with new developments throughout the world. He not only read about them, he acted. On Jan. 12, 1847, at a meeting of the *Academie de medicine*, less than 3 months after Morton's success in Boston, Malgaigne announced that he had "etherized" 3 patients with great success; one patient, incompletely, and one without effect.[2] Velpeau had heard of ether inhalation anesthesia but had not yet tried

it. Malgaigne had administered the ether intranasally with an apparatus of his own design. Not only was he the first to use ether anesthesia in France, but he was also largely responsible for its rapid adoption throughout the country.

In 1835 Malgaigne joined the faculty of medicine and became a surgeon of the central bureau of hospitals, serving in turn at Bicetre, Saint Louis, and la Charité. He lectured on, and later published a book on, surgical anatomy.[3] In 1850 he succeeded to the chair of Professor of Operative Surgery, a position he held until his death in 1865.

Fig. 2.—Joseph François Malgaigne (1806-1865).

"He is a small man, quite stiff in figure and movements, but possessing good manners, and an intelligent, expressive countenance. He operates well and is a thorough master of surgery. His 'courage camarade' so frequently addressed to patients on whom he is operating, being pronounced in a military tone, and with a slight but pleasant accent, produces a very agreeable impression on those to whom it is addressed, and encourages them to bear with greater patience the suffering to which they are necessarily subjected." (Fig. 2)

Malgaigne's reputation today rests chiefly upon 3 of his books: *Manuel de médicine opératoire,*[3] *Traité des fractures et des luxations,*[5] and *Oeuvres complete D'Ambroise Paré revues et collationnee's sur toutes les editions avec les variantes.*[4] Having already discussed his great work on fractures and dislocations, a brief comment on the others is in order.

Manuel de médicine opératoire, published in 1834, is a pocket-sized volume of almost 800 pages. Surprisingly enough, although devoted entirely to the description of operative methods, it does not contain a single illustration. The words securité, simplicité, celerité, on the title page emphasize the guiding principles used in selecting the various operative techniques described in the text. Only the safest, most simple and most rapid means of accomplishing the desired ends are espoused. This was not an original work in any sense. What distinguishes this book from the pedestrian compilations of many other authors is the discrimination with which Malgaigne chose his material, the critical way in which it is evaluated, and the clear, concise manner in which the essence of the subject is distilled onto the printed page. The book was a great success and quickly appeared in English, German, Spanish, and Italian translations. An edition in Arabic was even published. Of the fourth French edition of 1841, Stewart[9] says: "This is the best manual published on the subject of operative surgery. It contains a complete résumé of all of the various methods and processes in use, and is the standard manual on this subject in France." It remained so for 30 years.

Malgaigne's edition of the complete works of Ambroise Paré[4] was an attempt to produce, as Littré had done for the works of Hippocrates, a definitive edition. In this he succeeded admirably. It was a task of great complexity, for Paré had had a long life as a writer (1545-1590) and during this time had not only discussed a tremendous variety of subjects but had modified and changed his opinions and doctrines continuously. The entire body of Paré's writing is arranged and ordered with great skill. It is possible to follow the development of Paré's ideas on any subject to their final form. A complete subject index multiplies the value of the collection.

A considerable portion of the first volume is devoted to an introduction which consists of a history of surgery in western Europe from the sixth to the sixteenth century, ending with a biography of Paré and a discussion of his work. This introduction is one of the finest short accounts of the history of surgery extant. It is unfortunate that it was not published separately since it stands in the shadow of the immensity of Paré's achievement and for this reason has not received the attention which is its due.

John Shaw Billings, American surgeon and historian, epitomizes the career of Malgaigne: "Malgaigne was the greatest surgical historian and critic the world has yet seen, a brilliant speaker and writer, whose native genius, joined to incessant labor, brought about a new mode of judging of the merits of surgical procedures,—the mode of statistical comparison joined to experiment. He was not a great operator, and although he made some improvement in the art, such as his hooks for the treatment of fractures of the patella, his suggestion of suprathyroid laryngotomy, and so forth; these are of small importance as compared with his work of exploding errors, exposing fallacies in reasoning, and bringing to bear upon the work of the present day the light of the experience of the past, of which his treatise on fractures and dislocations affords many excellent examples."

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Book Review

CONDUCTED BY J. GARROTT ALLEN, M.D.

Plastic Arterial Grafts. W. Sterling Edwards. Springfield, Ill., 1943, Charles C Thomas. $4.50.

Dr. Sterling Edwards has given us in this book a review of the development and present usefulness of crimped nylon grafts. One chapter of this book discusses in considerable detail this most important principle now being used with increasing frequency in the employment of synthetic arterial grafts. Around this he has attempted to cover the general problem of plastic arterial grafts, outlining the history and discussing the various forms of plastic materials undergoing study in this field. About all one could have asked at this point would be more data on the extent of use and results with these various materials by other men working in this field. The story of the crimped nylon grafts as worked out with Dr. Tapp of the Chemstrand Corporation is given well with excellent photographs of procedures and methods of handling this type of nylon graft. Following this is a discussion of arterial injury and repair which is well done and especially points out the rare usefulness of a tourniquet and the enigma of sympathectomy and nerve block in the treatment of these injuries. There is a discussion of arteriovenous fistulas which is surprisingly vague with very little preliminary discussion.

The methods of handling arterial aneurysms and arterial obstructions with the use of the crimped nylon grafts are presented in some detail. This is the clinically useful portion of the book. The conclusion of the book covers speculations on the use of these grafts in thoracic aortic surgery. It also summarizes the future problems in this field such as the development of nonsuture techniques, replacement of the superior vena cava and other large veins, causes of delayed thrombosis in plastic grafts, and the production of new and/or better plastic materials. Unfortunately none of the physiology and physics of flow relations in grafts is presented.

—Peter V. Moulder